CORTICAL REPRESENTATIONS OF BODY PARTS IN CHILDREN AND IN INDIVIDUALS BORN WITH MISSING HANDS

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by

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Picture on front page:

Woman's hand from Leonardo da Vinci

PREFACE

The various representations of the human body in the brain enable bodily movements and perception as well as an intact interaction with our environment. To deal with the issue of these body representations from a neuroscientific point of view was a very exciting and enriching experience. I studied in the last years the body representations in the brain in respect to developmental and pathological changes and therefore experimentally examined normally limbed children and adults as well as persons with missing limbs since birth. Not only did they help me to answer academic questions, but more importantly they also showed me that the quality of life is independent of one's physical appearance.
I am immensely grateful to these children, amelic persons and members of the control group for their kind participation in the experiments.

My special thanks then goes to my supervisors, Professor Dr. rer. nat. Friedrich Wilkening (Department of Experimental and Developmental Psychology, University of Zurich), Professor Dr. phil. Marianne Regard and PD. Dr. phil. Peter Brugger (both Neuropsychology Unit, University Hospital of Zurich). They supported my research in this field, guided me patiently through my dissertation and offered me the benefit of their broad experimental, developmental and clinical neuropsychological experience and knowledge. Additionally, I would like to thanks to my co-advisors Professor Dr. phil. Marie-Claude Hepp Reymond and Professor Dr. med. Spyros Kollias as well as to the co-authors of the publications included in this thesis for the lots of fruitful discussions and the great helpfulness.

I also wish to thank the whole team of the Neuropsychology Unit, Neurological Department, University Hospital of Zurich who has created a friendly and inspiring atmosphere to work in.

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1. ABSTRACT

The present thesis addressed the cortical representation of body parts in normally limbed children and adults as well as in individuals born with missing hands. With the application of behavioral, neuropsychological and neuroimaging methodologies in different populations, i.e. healthy normally limbed adults and children as well as participants with limbs missing since birth, this issue could be examined in a broad scientific context. The four studies of my thesis investigated the following questions, each addressing different aspects of body representation: (1) Does a congenital absence of a limb (so-called amelia) cause somatotopical alterations of the body representation in the primary motor cortex; (2) do amelic patients present with measurable abnormalities in higher-order body representations (e.g. body schema) as measured by motor imagery tasks; (3) does lifelong experience of phantom sensations of these missing limbs relate to changes in the body schema; (4) is there a developmental effect of the body representation in the healthy brain, i.e. do children differ from adults in performing a motor imagery task assessing components of the body schema?

The results of the first study revealed a significantly altered topological organization of the primary motor cortex in participants with unilaterally missing hands as compared to normally limbed controls. The second study showed that children's body schema is highly influenced by visual and, even stronger by proprioceptive inputs, whereas in adults, both, visual and proprioceptive sources affected the body schema in a comparably strong way. The results of study 3 and 4 are consistent with each other insofar as they suggested (1) that in subjects with one hand missing since birth the lifelong use of the other, existing hand facilitates motor imagery regarding the missing hand. (2) Furthermore, in participants with bilaterally missing hands, the presence of phantom sensations could be shown to favor motor imagery regarding congenitally absent limbs.

These findings are highly relevant, clinically as well as for the basics of neurosciences, as they provide converging evidence for cerebral plasticity, which is in turn a precondition for neuro-rehabilitation. Moreover, the behavioral and anatomical research in amelic participants provides a unique, natural model to investigate the development and the topography of body representations. It could also be helpful for the understanding of the genesis of phantom sensations in congenitally or traumatically absent limbs.

2. GENERAL OVERVIEW

This thesis comprises four experimental studies investigating the representation of the hand in the human brain. More precisely, developmental and pathological aspects of the primary motor and of the higher-order hand representation were assessed on the behavioral level as well as with studies conducted to image the relevant brain areas. The general background for the interest to study different body representations in the brain comes from clinical observations documenting dysfunctions either in the primary motor cortex or in association areas important for the body schema.

Study 1 deals with the plasticity of the body representation in the primary motor cortex of persons with an absent body part since birth, Study 2 focuses on the higher-order body representation in healthy children, and in Study 3 and Study 4 also the higher-order body representation was examined but again in patients with congenitally missing limbs. In the following, a brief theoretical introduction is presented as the basis for discussing the results of my four studies.

2.1. Body representations in the brain

As aforementioned, the body is represented several fold in the human brain. On one hand, there are the so-called “somatotopical” body maps in the primary motor and in the somatosensory cortex, reflecting the distribution of the motor and sensory receptors of the body parts. On the other hand, there is a higher-order, more cognitive representation of the body in the brain important for the body schema. By the way, another area important for body sensation and representation in the thalamus will not be discussed.

2.1.1. Body representation in the primary motor cortex (Study 1)

The primary motor area comprises the precentral gyrus and the related cortical tissue that folds into the central sulcus between the frontal lobes and the parietal lobes. Scientists have long considered the arrangement of the primary motor area to be about the same in all mammals. In neurological terms, the area is described as M1.

The beginning of the exploration of the somatotopic body representation in the primary motor cortex (further on "M1") can be traced back to mid 19th century. It was

John Hughlings Jackson (see Figure 1) who provided us for the first time with a comprehensive theory of how the brain controls muscles. He postulated a systematic neuronal organization of the cortical region controlling movements of body parts. His notion came from the observation of focal motor seizures (so-called "Jacksonian" epilepsy) in his wife and his cousin. He observed that the epileptic seizures were electrical discharges in the brain by carefully recording the course of his wife's seizures. They seemed to always follow a stereotypical pattern starting with motor discharges in one of her hands, moving to her wrist, then her shoulder, then her face. It finally affected the leg on the same side of her body, and then stopped (Jackson 1875, in Taylor 1958). Consequently, he argued that M1 is divided into circumscribed sections, each of them being responsible for controlling the specific body part.

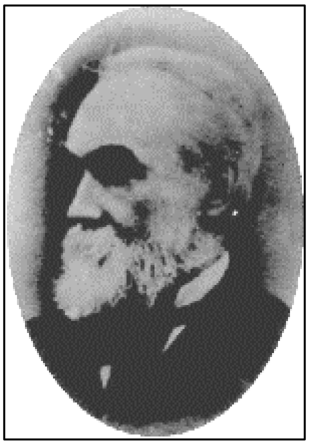

Figure 1. J.H. Jackson, 1835-1911

As techniques for electrical stimulation improved, various maps of body part representation in M1 were developed culminating in the most famous up to date, the Penfield's motor homunculus, i.e. Latin for "little man" (Penfield & Rasmussen, 1950). Penfield (see Figure 2) gathered his data by electrically stimulating the surface of the brain in patients with epilepsy to localize seizure focus.

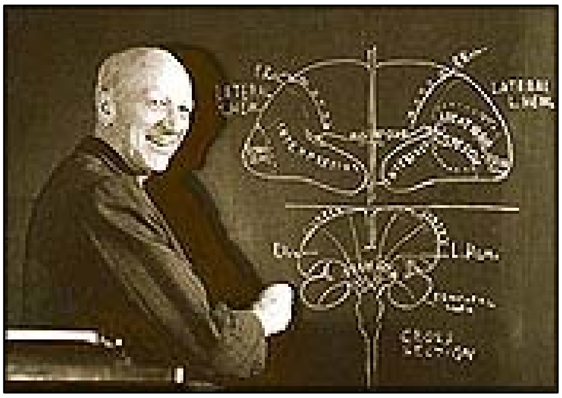

Figure 2. Wilder Penfield developing a map of the brain. Photo: Princeton University Press.

Remarkably, in this "motor map" certain body parts, namely those making the finest movements such as the face, mouth and fingers, take up much more space than others such as the trunk. The bigger the body part is displayed in the Figures 3 and 4, the more neuronal space is occupied to control it.

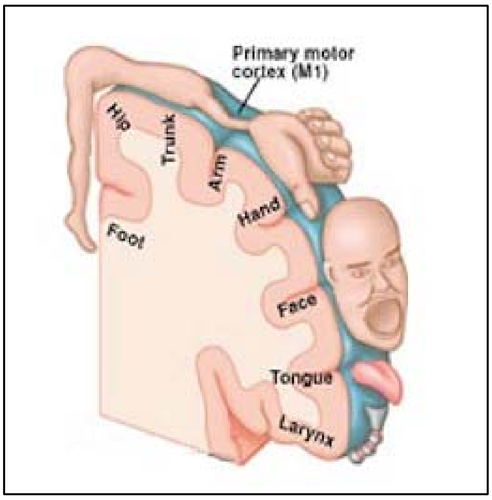

Figure 3 (left side). Penfield's motor homunculus, representation of a miniature human being.
Figure 4 (right side). Body part representation on the surface of M1.

Both, the motor and the somatosensory[1] homunculus are hence maps of the proportionate association of the cortex with the body parts.

Similar to other brain areas the motor homunculus undergoes ontological changes so that a child's one differs significantly from an adult's one. Once fully developed, the adults' motor homunculi are generally highly comparable. However, several factors can induce changes of the somatotopical organized M1 surface. For example, in healthy subjects, an intensive training of specific motor skills like piano playing (Münte, Altenmüller & Jäncke, 2002), playing volleyball (Tyc, Boyadjian & Devanne, 2005) or racquet (Pearce et al., 2000) was found to alter the functional organization in the relevant M1 body representation. These examples indicate that the representation is plastic and changes according to the overlearned skill. Moreover, selective patients with diseases affecting the central nervous system (e.g. brain injuries) or the peripheral nervous system (e.g. pain, congenital or traumatic amputation, spinal

[1] The homunculus in the primary somatosensory cortex describes the relative sensory space that our body parts occupy on the cerebral cortex. The lips, hands, feet and sex organs are considerably more sensitive than other parts of the body, so that the homunculus has grossly large lips, hands and genitals. It also reflects kinesthetic proprioception, the body as felt in motion.

cord injury) pose an interesting model of nature to study dynamic changes in the cortical body areas (see Flor et al., 1995 with traumatic amputees; Sanes & Donoghue, 2000 for an overview of M1 plasticity; Nudo, Plautz & Frost, 2001 with motor cortex damaged patients; Curt et al., 2002 with spinal cord injured patients; Cruz et al., 2003 with traumatic and congenital amputees; Elbert & Rockstroh, 2004 for an overview of reorganization of the human cerebral cortex). Another interesting model are the few patients with surgical extension of lower extremities or bilateral hand transplantation also showing modified organization of the primary somatosensory (further on "S1") cortex (Giraux et al., 2001; Di Russo et al., 2006).

In the context of this thesis, studies concerning the plasticity of M1 in subjects suffering from a congenital or a traumatic amputation are of special interest. Results from recent studies of traumatic upper limb amputees showed that an extensive reorganization of both the M1 and S1 is not manifest in all amputees, but only in those suffering from phantom pain. In the hemisphere contralateral to the amputated limb, a significant shift of the mouth representation towards the adjacent deafferented hand area in M1/S1 was observed (e.g. Karl et al., 2001; Lotze et al., 2001). In contrast, for lower limb amputees an altered motor body part representation was shown in the hemisphere ipsilateral to the missing limb. Furthermore, there was no correlation of the cortical reorganization and phantom pain intensity as has been reported in upper limb amputees (Flor et al., 1995 in upper limb amputees; Schwenkreis et al., 2003 in lower limb amputees).

People with a congenital absence of a complete body part (i.e. amelia) have been examined with different brain imaging methodologies for their primary somatosensory map, but not with respect to the M1 organization. In subjects with unilateral hand amelia the adjacent orofacial areas did not invade the somatosensory hand area; a result comparable to that of traumatic amputees without phantom sensations or phantom pain. Thus, it was assumed that congenital absence of a limb does not lead to a cortical reorganization (Flor et al., 1998; Montoya et al., 1998). This assumption turned out to be incorrect. Only recently, a significant reorganization of S1 was reported for one subject with a bilateral arm amelia who did also not report any phantom sensations or phantom pain (Kamping, Lutkenhoner & Knecht, 2004).

Obviously, subjects who miss one or several body parts since birth provide a unique opportunity to study the development of M1, an issue not reported in literature but treated here in Study 1.

2.1.1.1. Method applied in Study 1

In the Study 1 we made use of the functional magnet resonance imaging (fMRI) method. The advantage of this method over other imaging methods enabling neuroscientists to see inside the living brain is the non-invasiveness. fMRI is a special appliance of the common magnet resonance imaging (MRI), which will be briefly described: MRI is a non-invasive procedure that uses powerful magnets and radio waves to construct pictures of the body including the brain. Unlike computer tomographic imaging, which makes use of potentially harmful radiation, MRI is based on the innoxiously magnetic properties of atoms. The physical principles of MRI determining its signal characteristics that are the basis for forming the brain images should be presented in a few words: A person is placed into the MRI scanner, a tube surrounded by a giant circular magnet producing a strong and homogeneous magnetic field. Various atomic nuclei, particularly the proton nucleus of the hydrogen atom, align themselves with this field and reach a thermal equilibrium. The subject is thereby "magnetized." The proton nuclei precess about the applied field at a characteristic frequency, but at a random phase (or orientation) with respect to one another. Application of a brief radio frequency electromagnetic pulse disturbs the equilibrium and introduces transient phase coherence to the nuclear magnetization that can, in turn, be detected as a radio signal and formed into an image.

If the MRI is processed while a mental task is given to the subject, fMRI images can be generated. FMRI determines the neurobiological correlate of behavior by identifying the relatively specific parts of the brain that become active during the performance of the specific task in vivo. It measures signal changes namely tiny metabolic changes in the brain that are due to changing neural activity. More precisely, neural activity is always accompanied by an increase in blood flow to the local vasculature resulting in a corresponding local reduction in deoxyhemoglobin as the increase in blood flow occurs without an increase of similar magnitude in oxygen extraction. Applying complicated physics and statistics enables ones to make these changes of the blood-oxygen level visible in images, which are well interpretable.

MRI and fMRI not only make possible to look closely at the anatomy of the brain, but also help determine precisely which part of the brain is handling critical functions such as thought, speech, sensation and, most important for our studies, movements. In studies considering body part representation in M1, the subjects' task is, in the majority of cases an execution of a voluntary, repetitive movement with the examined body part. FMRI makes the neural substrates underlying the body part movement visible. Figure 5 displays the neural activity of a hand movement. The red blobs indicate the neural activity underlying an opening and closing movement with the right hand of a healthy subject.

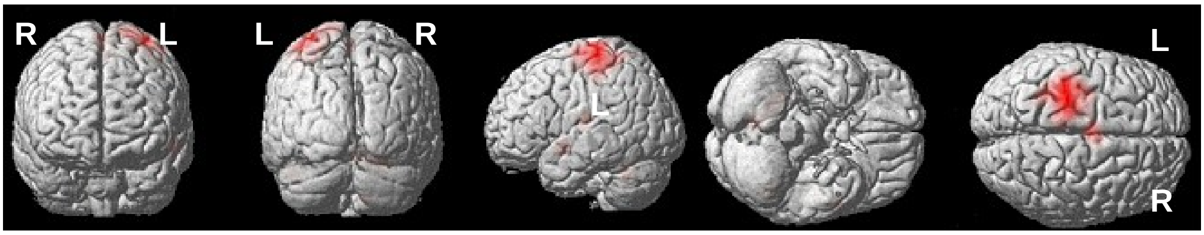

Figure 5. Human hand representation as revealed by fMRI (Funk et al., unpublished data).

Mapping the different body part (food, hand, mouth, tongue etc.) representations of an individual subject allows conclusions about the somatotopic organization of its M1. Countless such studies focusing on the somatotopy of M1, in healthy as well as in pathological populations were conducted to date (for an overview: Mattay & Weinberger, 1999).

2.1.1.2. Participants investigated in Study 1

In Study 1, we examined persons with amelia. Amelia is a very rare birth defect marked by the complete absence of one or more limbs. According to the number of missing limbs, terms like tetra-amelia (the absence of all four extremities) are used. We studied the somatotopy of M1 in eight subjects with unilateral upper limb amelia namely of the hand (further on called "unilaterally amelic participants"). The participants were recruited by flyers, personal contact or by a self-help group for amelic persons (see www.pinocchio.ch).

Five of the eight unilaterally amelic participants were born without a left hand (three men, age: mean=32.0, sd=5.7 yrs) and three without a right hand (all men, age: mean=26.7, sd=4.5 yrs). Interestingly, in our sample as well as reported in literature left-sided body part amelia develops more frequent than right-sided. The reason for this interesting observation has not been addressed. The etiology of amelia remained unknown in all participants; none has suffered form thalidomide embryopathy[2]. A common answer of the participants describing the handicap was "a freak of nature". No participant had additional physical disabilities beside the missing hand, nobody had a history of neurological or psychiatric affections and no one met an exclusion criterion for fMRI scanning (e.g., metallic implants that are ferromagnetic) which are listed in Appendix 1. Importantly, they never experienced phantom pain or other phantom sensations in the missing hand.

The control group consisted of nine healthy subjects matched for age and gender.

2.1.2. Higher-order body representations (Studies 2-4)

Besides the body representation in M1 other higher-order, cognitive body representations exist. Schwoebel and Coslett (2005, p. 543) very plausibly described them:

> *"Consistent with classic accounts suggesting multiple representations of the human body (e.g., Pick, 1922; Head & Holmes, 1911–1912), recent evidence suggests that there are at least three distinct types of body representations. The first, termed the body schema, is a dynamic representation of the relative positions of body parts derived from multiple sensory and motor inputs (e.g., proprioceptive[3], vestibular, tactile, visual, efference copy) that interacts with motor systems in the genesis of actions (e.g. Schwoebel, Boronat & Coslett, 2002). The second representation, termed the body structural description, is a topological map of locations derived primarily from visual input that defines body part boundaries and proximity relationships (e.g. Buxbaum & Coslett, 2001; Sirigu, Grafman, Bressler, & Sunderland, 1991). The third human body representation, which has been called the body image or body semantics, is a lexical–semantic representation of the body including body part names, functions, and relations with artifacts (e.g. Coslett, Saffran & Schwoebel, 2002). Several converging lines of evidence support the*

[2] Severe limb anomalies, usually amelia or very severe proximal phocomelia, often associated with flipper-like digits in the shoulders and hips, representing the distal limb. Associated with maternal thalidomide ingestion during early pregnancy.
[3] Proprioception is the ability to sense the position, location, orientation and movement of the body and its parts.

> *psychological validity of and distinctions between these three types of human body representations."*

In the context of this thesis, only the body schema will be discussed. Haggard and Wolpert (2005) described the single components involved in the body schema:

> Spatially coded: The body schema represents the position and configuration of the body as a volumetric object in space.
>
> Modular: The brain represents different body parts in different neural modules, using the resulting modular network to represent all postures.
>
> Updated with movement: Continuously tracking the positions of the body parts.
>
> Adaptable: The body schema must adapt to allow for gradual changes in the spatial properties of the body as for example body parts change over the life span.
>
> Supramodal: The body schema receives multiple sensory inputs. A visual and a tactile stimulus at the same location on the body surface may form a joint representation within the body schema (Rorden et al., 1999).
>
> Coherent: The brain maintains a coherent spatial organization of the body scheme across space and time. This ensures a continuity of body experience, which may play a major role in individual self-consciousness.
>
> Interpersonal: A body scheme represents both one's own body and the bodies of others. If we want to perceive changes in a model's body posture, it's easier if we move our own body simultaneously.

An additional property, which may be important, is that the body schema does usually not enter into awareness.

There are at least two main sensory inputs providing an on-line feedback to the body schema, namely vision and proprioception. The exact manner of integration of these two sensory inputs remains unclear. Two pathological conditions help to illustrate the different inputs on the body schema of the visual or proprioceptive system: subjects without any proprioceptive inflow (e.g. the case of a subject IW, described in Gallagher & Cole, 1995) and subjects without visual input (i.e. blind people). IW suffered from acute sensory neuropathy (destruction of large fibers below the neck) resulting in the lack of both proprioceptive function and sensation of touch below the neck. Despite the loss of proprioception, IW recovered movement control, relying heavily on attentive visual cues. That is, there was no recovery of proprioceptive sense, but compensation by cognitive control, i.e. attention and vision was successful in rebuilding a partial body schema. In contrast blind people can achieve accurate sensorimotor control without such effort. This suggests that the proprioceptive updating of the body schema is largely automatic, not so the visual updating.

Notably, alterations of the body schema caused by pathologies in the sensory input system, such as deafferentation[4], deefferentation[5] or severe limb pain has already been widely reported (Gallagher & Cole, 1995; Melzack et al., 1997; Schwoebel et al., 2002). Moreover, interesting cases to study the functional organization of the body schema are phantom sensations in both traumatic and congenital amputees.

The Studies 2-4 of this dissertation also dealt with the question of how alterations in the sensory inflow, caused by developmental or pathological changes, affect the body schema. For the first time potential affections on the body schema's development caused by the factors "age of an individual" and "absence of proprioception since birth" have been experimentally [thus without any suggestibility] investigated. For treating this issue, children (Study 2), amelic subjects (Studies 3 and 4) and healthy, adult controls participated in neuropsychological tasks assessing the body schema. Important for the theoretical background of behavioral tasks assessing the body schema is the observation that not only the execution of movements but also their mere imagination, observation, imitation and recognition rely on the body schema. Neuropsychological methods investigating the body schema, thus also comprise investigations of the imagination and recognition of human body parts and movements. Notably, all three studies were based on two general premises (1) the body schema develops over life span and (2) the body schema depends on an individual's sensory experience in both proprioceptive and visual terms.

Finally, it should be reported that the knowledge of the anatomical areas involved in the maintenance of the body schema largely comes from the clinical literature (for a classical treatment of the issue see Critchley, 1953). Patients suffering from disturbances of some kind of body schema representation are usually found to have lesions in the parietal lobes, particularly its inferior part. Lesions in the right parietal lobe as for instance in the syndromes of neglect (Coslett, 1998) and anosognosia (Berti et al., 2005) may typically result in the unawareness of body parts and sensations,

[4] The elimination or interruption of sensory nerve impulses by destruction or injury of the sensory fibers from periphery to center

[5] The elimination or interruption of motor nerve impulses by destruction or injury of the motor fibers from center to periphery

while lesions in the left parietal lobe may produce difficulties in the identification of body parts as typically in the Gerstmann syndrome (Gerstmann, 1930)

2.1.2.1. Method applied in Studies 2 and 3

In Studies 2 and 3, we used a slightly modified version of the hand laterality task introduced by Cooper and Shepard (1975). As the original task, our modified task assesses the recognition of rotated body parts, more precisely the hands. Subjects had to decide as fast and correctly as possible whether a presented stimulus depicts a right or a left hand (laterality decision). Right and left hands, palms and backs of hands were presented in one of six possible orientations (from 0° to 300° in 60° steps, clockwise), in our version stimuli were presented in one of four possible orientations (from 0° to 270° in 90° steps, clockwise).

Up to date, different studies (Sekiyama, 1982; Parsons, 1987; Parsons, 1994) investigated and replicated the response pattern in the hand laterality task, for the fist time described in Cooper and Shepard (1975). In healthy subjects, the time required to make a laterality decision of a rotated hand (is it a right or a left hand?) was shown to be identical to the time required to perform the actual hand movement. Moreover, the duration of both the mental and the physical hand rotation from the actual hand position into the displayed stimulus hand position is determined by the angular orientation of the stimulus and its kinesthetic[6] properties. To specify, the reaction time to a given stimulus increases with the distance of rotational angle from 0º and, with the degree of awkwardness of the presented hand position (e.g. Parsons, 1987). Furthermore, response patterns of rotated hands bear the following characteristics: (1) Right-handers recognize their dominant (right) hand more easily, while left-handers do not show a side preference (Gentilucci et al., 1998). (2) Backs of hands are faster recognized than palms, at least when presented in rotation angles between 0º and 120º clockwise and counter clockwise. If hand stimuli are presented upside down (i.e. fingers pointing down, 180º), palms are faster recognized (Parsons, 1987). (3) Both, the mental and the actual rotation of a hand toward the body's midsaggital plane, i.e. a medial movement, require less effort and time than a rotation away from the body's midsaggital

[6] Kinesthesia: (1) the perception of body position, movement and muscular tensions, (2) the ability to feel movements of the limbs and body.

plane, i.e. a lateral movement (Parsons, 1994). The general explanation for these performance characteristics is the notion that participants mentally rotate their own hand (starting at the actual hand position during the task) according to the position depicted in the stimulus presented, i.e. they mentally rotate their left hand in the position of a left and their right hand in the position of a right stimulus hand. A rapid pre-conscious perceptual analysis of the stimulus is meant to guide the participant to imagine initially the hand that turns out to match the stimulus. Most important, caused by the kinematic configuration of the body that is represented and transformed in the mental simulations of movements (in our case a mental rotation), the representation underlying the task performance is the body schema.

Mental rotation, of objects and body parts, shares to some degree the neural substrates activated by a real, physical rotation. A large number of brain imaging studies have identified activations in the primary motor and premotor cortex during mental object and body part rotation (Cohen et al., 1996; Kosslyn et al., 1998; Tagaris et al., 1998; Zacks et al., 1999). Moreover, Ganis and co-workers (2000) showed that inhibition of the electrical activity in the primary motor cortex, induced by transcranial magnetic stimulation, significantly slowed down mental rotation.

Various patient groups have been studied with such hand laterality tasks. Patients suffering from severe limb pain, for instance, showed significant longer reaction times to hand stimuli depicting the affected hand as compared to stimuli depicting the unaffected hand. These findings suggested that the body schema is influenced by pain and that the hand laterality task may provide an objective measure of the dysfunction (e.g., Schwoebel et al., 2001; Schwoebel et al., 2002). Not only pain but also an amputation of the dominant hand has been shown to alter the task performance (Nico et al., 2005). These examples illustrate that peripheral and central dysfunctions affect the performance in the hand laterality task, said to assess the body schema. On this background, we therefore designed Study 2 and Study 3.

2.1.2.2. Participants investigated in Studies 2 and 3

2.1.2.2.1. Children

In Study 2, 24 healthy children, 13 boys and 11 girls, from two kindergartens (St. Martin in Zurich and Wassergass in Horgen) aged between 5 years 5 months and 7 years 2 months were examined. Exclusion criteria were neurological affections especially perinatal complications, loss of consciousness including seizure-induced. Any medications affecting cognitive performance were also considered a reason for non-inclusion. All parents gave written informed consent. The result of 22 children could be analyzed[7]. All 22 children showed a clear right hand preference according to the criteria in the developmental neuropsychological assessment battery (NEPSY by Korkman, Kirk & Kemp, 1998, see Appendix 2). For assessing the handedness each child had to spontaneously a) draw a circle, b) point with a finger at a yellow ball among other colored balls, c) put the yellow ball on a stick, d) catch the pink ring among other colored rings and e) throw the pink ring into a box.

2.1.2.2.2. Unilaterally amelic participants

In Study 3, fourteen persons with a unilateral hand amelia were examined in respect to their higher-order body representation. Nine (5 women) had a congenitally absent left hand (age range 8 to 33 yr, mean=17.4, sd=8.7 yrs) and five (2 women) a congenitally absent right hand (12 to 27 yr, mean=20.6, sd= 5.7 yrs). Some of the subjects participated already in Study 1. Etiology of amelia is unknown in all subjects and none had any additional physical disability. None had experienced any phantom sensations including phantom pain in the missing limb during waking life. Figure 6 displays a man with a left hand amelia performing the hand laterality task assessing the body schema.

[7] One child was excluded because of insufficient understanding of the task instruction (foreign language) and the other one had insufficient attention span.

Figure 6. A participant with unilateral amelia of the left hand.

2.1.2.2.3. Bilaterally amelic participants

In Study 3 (and Study 4) we assessed two unique subjects with bilateral amelia of the hands. As one of them reported phantom body sensations the issue of "aplasic phantoms"[8], i.e. phantom sensations of congenitally missing body parts, should briefly be addressed. A phantom limb is a subjective feeling of the ongoing presence of a limb that does no longer physically exist. Phantom limb sensation and phantom limb pain were predominantly described in subjects with a traumatical amputation as they occur in 80-100% of the amputated limbs whereas 50-80% of those sensations are painful (Sherman et al., 1984; Jensen et al., 1985). Phantom sensations can occur in different modalities such as movement, temperature, touch and pain and can be triggered by a variety of stimuli, including pressure on the stump, emotional distress, and even changes in the weather (Ramachandran & Hirstein, 1998). Even though the mechanisms underlying both painless and painful sensations are widely discussed, their neurophysiological basis remains unresolved (Grouios, 1998). One explanation of phantom sensations suggests that the body schema, assumed to be plastic, is strongly involved in the development of phantom sensations. This notion is supported by empirical evidence showing that both, sensory inputs and proprioceptive feedback playing an important role in the development of the body schema and hence in the

[8] "Aplasia" indicates that an organ or tissue did not fully develop. Related terms are amelia/dysmelia, which refer to the complete/partial absence of skeletal parts of a limb, and phocomelia, indicating the attachment of a hand/foot directly to the trunk or to the upper arm/leg. Thus, theories on "aplasic phantoms" also subsume theoretical explanations of the existence of phantom sensations in amelic participants' missing limbs.

genesis of phantom sensations in amputated limbs. However, these sensory-based theories are unable to account for the existence of phantom sensations in congenitally missing limbs. Moreover, in contrast to the idea that sensory inputs are essential to generate a body schema, the existence of aplasic phantoms suggests that the body schema might be genetically predetermined and merely strengthened by sensory experience (Melzack et al., 1989).

Actually, both the mere existence of aplasic phantoms and its probable neurophysiological basis are still matter of debate in neuroscience. Although the physiologist Gabriel Gustav Valentin documented a number of cases of aplasic phantoms as early as 1836 (Valentin, 1836), it is only within the last half century that the issue of aplasic phantoms has seriously been investigated. During the second half of the 20th century, more reports of aplasic phantoms surfaced in the literature. Some were single case studies, for instance Poeck's (1964), however, beginning with Simmel (1961; n=27) and Weinstein and Sersen (1961; n=30), group studies were also published, which allowed the first rough estimation of the incidence of phantoms among persons with limb aplasia. Different authors' estimates depended on the exact definition of what constituted a "phantom" and varied between around 6% (1 out of 17 subjects; Burchard, 1965) to 18% (13 out of 71 subjects; Weinstein et al., 1964). This latter figure comes close to the 20% incidence reported in the largest group study ever published (15 subjects with phantoms in 76 people born with absent or malformed limbs, Melzack et al., 1997).

The manifestations of the aplasic phantom are as heterogeneous as their explanations. There is a wide spectrum of potential explanations: on one hand, aplasic phantoms are believed to evolve from an innate body schema, on the other hand they are believed to be the product of the suggestible mind. Common theories of the genesis of aplasic phantoms include the one by Pick (1915), who argued that aplasic phantoms do simply not exist, as the missing limb has never been represented in the body schema. Sohn (1914) and Skoyles (1990) accepted the existence of aplasic phantom even though they thought it to be a manifestation of wishful thinking, i.e. fantasy. For Simmel (1961), phantom sensations could only appear in patients with little rudimentary preservation of distal body parts attached to the stump, as the aplasic phantoms were a product of stump characteristics [Simmel ignored the existence of phantoms in subjects with a pure amelia]. Burchard (1965) assumed aplasic phantoms to be a representation of the contralateral existing limb [he disregarded the existence of phantom sensations in subjects with bilaterally missing limbs since birth]. Finally, two theories suggested by Gallagher and co-workers (1998): First, aplasic phantoms are based on the existence of specific neural circuitry associated with innate motor schemas, such as the neural matrix responsible for early hand-mouth coordination. Second, aplasic phantoms are presumably modified by mechanisms that involve the reorganization of neural representations of the missing limb within a complex network involving both cortical and subcortical structures.

Even though the existence and genesis of phantom sensations are still discussed, we presume the existence of aplasic phantoms as indisputable. The comprehensive studies with subject AZ provided convincing evidence for this statement (e.g., Brugger et al., 2000).

AZ is one of the two bilaterally amelic subjects investigated in this thesis. AZ is a 52-year-old university educated woman who had been born without forearms and legs (reason of her tetra-amelia is unknown). Her upper arms are conically shaped and about 25 cm long (see Figure 7). Importantly, they lack any appendages representing rudiments of more distal parts of an upper limb. AZ skillfully uses her upper arms to steer her electric wheelchair, grasp objects, typewrite and eat (with the aid of a fork or spoon attached to a ring placed on her right upper stump). AZ reports that she has been aware of a complete body for as long as she can remember. Apart from her report, "objective" data supporting her subjective experience was provided (see Brugger et al., 2000).

Figure 7. Participant AZ having a tetra-amelia (with the courtesy of AZ).

The other subject, CL, a 43-year-old journalist, had bilateral hand amelia (including the shoulder articulations) and shortened legs, caused by thalidomide-related embryopathy (ref. to Figure 14C in section 3.3.3.1.1.). CL had never experienced any phantom sensations of his absent limbs.

As both subjects had bilaterally symmetric amelia and were otherwise healthy they could serve as one another's control.

2.1.2.3. Method applied in Study 4

In Study 4 we made use of another neuropsychological task assessing the body schema. The human awareness about bodily movements influences the perception of dynamic events. If we get incomplete information, the perceptual system even fills the information gap by drawing from motor knowledge[9]. With the help of this motor knowledge certain perceptual tasks (as for example the aforementioned hand laterality task) can be performed more efficiently. Another task also dealing with the influence of motor knowledge on human movement perception is the task on visual apparent motion of limbs by Shiffrar & Freyd (1990). In Study 4, we used a minimally modified version of this task. In the original as well as the modified task, observers watch pairs of photographs depicting a human model performing simple actions. The two photographs that differ only in the position of one limb segment relative to a joint were presented in rapid alteration with constant exposure durations of 90 ms (see Figure 8).

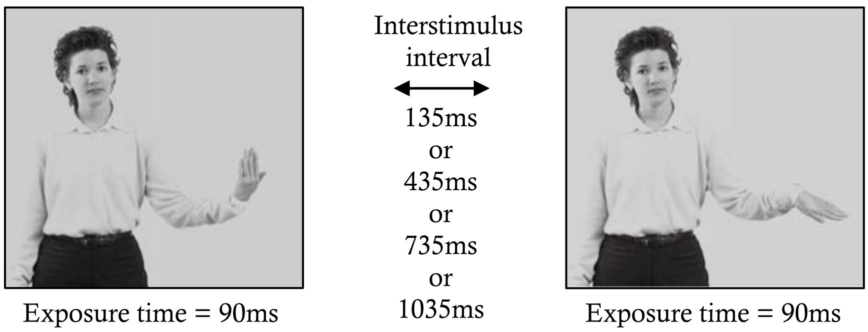

Figure 8. Sample stimulus pair in the task on visual apparent motion of limbs.

[9] Our exquisite sensitivity to biological motion must have given us some evolutionary advantage, and it is likely to involve specific, innate expectations and prejudices concerning bodily movements that are as deeply entrenched as those that modulate apparent motion.

The rapidly altered presentation of these two photographs gives rise to an apparent motion percept (by choosing stimulus onset asynchronies (SOAs) between 100 ms and 750 ms, Shiffrar and Freyd (1990) elicited in about 90% of the subjects an apparent motion perception). As long as the two photographs are flashed in rapid succession (SOAs between 150ms and 350ms), normal observers invariably perceive the displaced limb traversing the shortest possible path of visual apparent motion. Execution of a limb movement along this seen trajectory is, however, not anatomically possible as it would violate natural joint constraints. As the presentation rate slows (SOAs between 350ms and 750ms) observers increasingly perceive paths of apparent limb movements that follow natural human limb trajectories as apparently the stored kinaesthetic knowledge about possible movements constrains the visual perception.

To sum up, the task on visual apparent motion of limbs suggests a competition between two (sensorimotor and visual inputs) biasing factors. At short SOAs, the prevailing factor is visual input that elicits the preference for shorter paths. Instead, at long SOAs body perception becomes penetrable by cognitive (somatosensory and motor) factors such as solidity and skeletal constraints. In line with this interpretation, neuroimaging data have revealed motor and parietal cortex involvement at slow, but not rapid presentation rates (Stevens et al., 2000).

2.1.2.4. Participants investigated in Study 4

In Study 4, we investigated again the two bilaterally amelic subjects AZ and CL (please see 2.1.2.2.3.). Their performance was compared to each other and to 6 normally limbed controls.

2.2. The four research studies

Table 1 illustrates the relation between the four experimental studies conducted in my dissertation.

Table 1. Displayed are the four experimental studies in respect to the investigated body representation, the used method and the examined population

Level of body representation	M1	Higher-order body representation (body schema)			
Method	FMRI	Hand laterality task			Task on visual apparent motion of limbs
Subjects	Unilateral amelics	Children	Unilateral amelics	Bilateral amelics	Bilateral amelics
Study	1	2	3	3	4

2.2.1. FMRI study on motor cortex organization in participants with an absent hand (Study 1)

The first study presented here (Study 1, see 3.1.) was designed to determine body part representation in the motor cortex of unilaterally hand amelic subjects: **Funk, M., Lutz, K., Hotz Boendermaker, S., Roos, M., Summers, P., Brugger, P., Hepp-Reymond, M.C., & Kollias, S.S. Alteration of the sensorimotor tongue representation in subjects with unilateral upper limb amelia. *Cerebral Cortex*, submitted.**

More precisely, the aim of the first study was to explore the amelic participants' area M1, especially that area directly linked to the control of hand movements (in normally limbed subjects) and the adjacent regions. For treating this issue, we assessed the sensorimotor tongue area both in unilaterally hand amelic subjects as well as in normally limbed control participants. We expected plasticity to be evidenced by invasion of the adjacent orofacial area into that "hand" area. By the way, studies conducted in traumatic amputees showed that the motor lip representation was shifted towards the deafferented motor hand area (Flor et al., 1998). Our results demonstrated that the neural activation pattern underlying tongue movement was considerably enlarged and displaced in the amelic subjects' hemisphere contralateral to the missing limb. This finding showed a cortical reorganization involving an enlargement of the sensorimotor tongue area and a shift towards the presumptive “hand“ area. Summarizing the results of Study 1, congenital absence of one hand alters the topological organization in the sensorimotor cortex.

2.2.2. Behavioral task assessing children's higher-order body representation (Study 2)

In Study 2 (see 3.2.) the development of the body schema in healthy children was assessed by a behavioral task requiring laterality decisions of rotated hand stimuli: **Funk, M., Wilkening, F., & Brugger, P. (2005). Motor processes in children’s imagery: The case of mental rotation of hands. *Developmental Science, 8,* 402-408.**

The assumption that a child's body schema differs from an adult's (see body schema components, especially "adaptable", as suggested by Haggard and Wolpert (2005) and introduced in 2.1.2.) led to the hypothesis of potential differences between the task performance of children and adults. Both, kindergarten children and adults performed the hand laterality task in two response conditions, once pressing the response buttons on the keyboard in a regular palm-down position, and once in a palm-up position. With this variation, we attempted to decouple the proprioceptive component from the visual one. Data analysis revealed that the recognition of the hand stimuli considerably depended on the subjects' hand posture. In fact, this effect was even stronger in children. This finding demonstrated that those aspects of the body schema that subserve the task performance are heavily influenced by the proprioceptive inflow, i.e. the actual hand position. Moreover, perceptual processes (as measured in the task) are even stronger linked to higher-order motor representations (e.g. body schema) in children as compared to adults. Study 2 thus revealed that the body schema of children depends more on proprioceptive input while the body schema in the mature adult brain relies as much on visual information.

2.2.3. Probing the body schema of subjects with congenitally missing limbs (Studies 3 and 4)

The purpose of Study 3: **Funk, M., & Brugger, P. Mental rotation of congenitally absent hands. *Brain and Cognition*, submitted,** and Study 4: **Funk, M., Shiffrar, M., & Brugger, P. (2005). Hand movement observation by individuals born without hands: Phantom limb experience constrains visual limb perception *Experimental Brain Research*, *164,* 341-346,** was to clarify the body schema of subjects with unilateral or bilateral hand amelia.

In contrast to the numerous experiments assessing both the body representation in M1 and the higher-order body representations in traumatically amputated subjects (e.g. Nico et al., 2005), results of amelic subjects have rarely been published. We experimentally investigated the body schema of amelic subjects using two behavioral tasks. One task, applied in Study 3, tested body part recognition (see 2.1.2.1.), and the other one, applied in Study 4, was about visual apparent motion of limbs (see 2.1.2.3.). Previous investigations applying these tasks in normally limbed participants revealed that an intact body schema facilitates or enables a regular task performance.

The results of Study 3 showed that the unilateral absence of a hand neither complicated nor affected laterality decisions of presented hand stimuli. Moreover, the performance of the unilaterally amelic subjects was comparable to that of normally limbed controls. Hence, we suggested that unilateral amelics exhibit a normal body schema for both, namely the absent and the existing hand. Another interesting result of Study 3 was the finding that the bilaterally amelic subject AZ performed in a comparable manner to that of normally limbed controls whereas the other bilaterally amelic subject CL showed an altered response pattern. The discrepancy in the task performance between these two subjects, we believed to be related to presence (like in AZ) or absence (like in CL) of phantom sensations of the absent limbs. Our finding, evidenced by the neuropsychological task solely, supports the assumption that aplasic phantoms require an intact body schema.

To further sustain this result AZ, CL and normally limbed controls also performed the task on visual apparent motion of limbs (Study 4). AZ showed the same flash rate-dependent perception of short vs. long apparent motion trajectories [this is a kinesthetically modulated perception of apparent limb motion] as individuals with limbs, while CL perceived the short, anatomically impossible trajectories at all interstimulus intervals. This finding, together with that of Study 3, indicates that AZ's but not CL's visual processing seems to be influenced by kinesthetic body schema information.

3. OWN CONTRIBUTIONS

3.1. Study 1: Alteration of the sensorimotor tongue representation in subjects with unilateral upper limb amelia

3.1.1. Abstract

We investigated the sensorimotor (S1/M1) tongue representation in nine normally limbed participants comprising the control group and in eight persons with a congenitally completely missing hand (i.e. unilateral hand amelia). All participants were examined by fMRI while performing horizontal tongue movements. The significantly activated clusters covering S1/M1 in both hemispheres were analyzed with respect to the number and intensity of activated voxels, as well as the location of the activation's centre of gravity (COG). In the right-handed control group, the number of activated voxels was significantly higher in the left as compared to the right hemisphere demonstrating left hemispheric motor dominance for horizontal tongue movements. In addition, the location of the left-sided COGs was significantly more medial and superior as compared to the right-sided ones. In the amelic subjects, no such hemispheric lateralization effect was observed. However, the neural activation pattern underlying tongue movement was considerably enlarged and displaced in the hemisphere contralateral to the missing limb when compared to the motor non-dominant, right hemisphere of the control group participants. We conclude that congenital absence of one hand leads to an appreciably altered topological organization in the sensorimotor cortex.

3.1.2. Introduction

The cortical and subcortical sensorimotor areas activated during simple and complex movements of the limbs have been extensively studied with fMRI and other functional neuroimaging methods. However, the movement and muscle artefacts (Marquart et al., 2000) producing perturbations in the homogeneity of the magnetic field (Yetkin et al., 1996) largely precluded fMRI experiments investigating voluntary motor performance of tongue, lip, jaw and eyes. Due to these methodological caveats, relatively few attempts to locate the sensorimotor tongue representation have been undertaken. One fMRI study focused on the cortical and subcortical regions activated during tongue contraction (Corfield et al., 1999), while other groups have investigated the neural substrates underlying motor activity of the tongue and their distinction or overlap with the cortical representation of the adjacent anatomical structures associated with swallowing and lip movements (Hesselmann et al., 2004; Martin et al., 2004).

More pertinent to the present study are reports on the possible asymmetry of the sensorimotor tongue representation in normally limbed subjects. It is beyond doubt that tongue movements are represented bilaterally in the primary sensorimotor (S1/M1) cortex lying in the inferior aspect of the homunculus, close to the lateral fissure (Penfield and Boldrey, 1937). The potential for lateralization remains unclear and is a subject of ongoing discussion. Wildgruber and co-workers (1996) reported strong bilateral activation during vertical tongue movements, without any statistically significant lateralization. In contrast, an asymmetrical motor tongue representation, defined by the number of activated voxels, was observed during the performance of horizontal (Hesselmann et al., 2004), as well as vertical movements (Lotze et al., 2000; Martin et al., 2004), albeit not always with satisfactory statistical confirmation.

The representation of oral motor structures has also been studied in the context of cortical reorganization in congenital or traumatic amputees and after spinal cord or brain injury (Curt et al., 2002; Cruz et al., 2003; Elbert and Rockstroh, 2004). Traumatic amputees suffering from phantom pain had extensive reorganization of both primary motor and somatosensory hand area by presenting a significant shift of the lip representation towards the adjacent deafferented hand area (Lotze et al., 2001). This cortical reorganization was interpreted as a neural correlate of phantom limb pain. In subjects with unilateral hand amelia (i.e. congenitally completely missing limb), only the organization of the primary somatosensory cortex has been investigated. As for traumatic amputees who had experienced neither phantom sensations nor phantom pain, there was no pronounced intrusion into the completely deafferented somatosensory hand area for these subjects (Flor et al., 1998; Montoya et al., 1998). However, a significant reorganization of the somatosensory cortex has been reported for one subject with bilateral arm amelia who did not report phantom sensations or phantom pain (Kamping et al., 2004). These authors raised the issue that cortical reorganization may be associated not only with the presence of phantom pain but may also result from extensive use of the body parts, which are cortically represented adjacent to the deafferented hand area. A use-dependent, rather than a malformation-induced reorganization has been further supported by a recent description of shrinkage of the somatosensory hand area, which was not proportional to the number of missing fingers in subjects with different degrees of upper extremity dysmelia due to thalidomide embryopathy (Stoeckel et al., 2005). However, the relation between the shrinkage of the hand area and the enlargement of the neighboring cortical areas was not examined. Thus, no clear conclusion regarding the organization of the sensorimotor cortex in subjects with congenitally absent limbs has yet been reached.

For this reason, we have investigated the sensorimotor tongue representation in a group of subjects who completely lack afferent input to the hand area due to a congenitally missing hand. We contrasted their motor homunculus with that of normally limbed control participants. The first question asked was whether hemispheric tongue dominance could be confirmed in nine normally limbed, right-handed participants forming the control group. Subsequently, we explored potential alterations of the normal sensorimotor tongue representation pattern in eight persons born with one hand missing. It was expected that the sensorimotor tongue representation in the amelic participants would be enlarged and displaced towards the deafferented hand area, thus being located more medial and superior, and that no hemispheric asymmetry should be evident.

3.1.3. Materials and methods

3.1.3.1. Participants

Seventeen volunteers (nine right-handed normally limbed subjects and eight unilaterally amelic participants) took part in this study. They all provided written informed consent for the participation in the experiment that was part of a study approved by the Ethics Committee of the University Hospital Zurich and conducted in accordance with the Declaration of Helsinki. The amelic group comprised eight subjects, the three of them with a congenitally absent right hand (all males, age: mean=26.7, SD=4.5 yr) and five with a congenitally absent left hand (three males, age:

mean=32.0, SD=5.7 yr). In all cases, the hand was completely missing, with no partial or residual appendages in evidence. Table 2 gives the age and gender of the amelic subjects, side and extent of amelia, as well as a summary of the subject's use (if any) of a prosthesis. No amelic subject had any other physical disabilities beside the missing hand, and the cause of amelia in their instance is unknown. None had ever experienced phantom pain or other phantom sensations. The amelic participants are listed in the same order in Table 2 and Table 4.

Table 2. List of amelic subjects with their individual characteristics.

Side of amelia	Extent of amelia	Prosthesis	Age	Gender	
right	below elbow	cosmetic	27	m	
right	only hand	no	31	m	
right	below elbow	cosmetic	22	m	
left	below elbow	cosmetic & myoelectic	37	m	
left	below elbow	cosmetic	39	m	
left	below elbow	cosmetic	28	f	
left	below elbow	cosmetic	26	f	
left	below elbow	myoelectic	30	m	

Nine young volunteers with normally developed limbs formed the control group, well matched for the age and education to the amelic group. The control group consisted of four females and five males (age: mean=30.0, SD=4.3 yr), all strongly right-handed as measured by the Edinburgh Handedness Inventory (Salmaso & Longoni, 1985; see Appendix 3).

Exclusion criteria for both the amelic and the normally limbed participants included medical (except for the limb malformation) or mental illness, head injury, substance abuse, and use of any medication affecting the central nervous system.

3.1.3.2. Experimental procedure

All subjects performed a horizontal tongue movement task. Tongue movements were investigated in preference to lip movements for the following reasons: (1) the tongue is almost always represented bilaterally, (2) it has a larger representation in the sensorimotor cortex than the lip (Hesselmann et al., 2004), and (3) tongue movements with closed mouth are less prone to inducing fMRI artefacts.

The tongue task was performed within a series of motor execution, mental imagery and observation tasks of hand, foot and tongue movements. The amelic participants performed the tongue task once, whereas the control participants performed the same task twice within two weeks. The repetition of the tongue experiment in the control group was performed to test the reliability and the reproducibility of the method in detecting and localizing the cortical tongue representation in S1/M1.

The motor tongue task consisted of three 21-seconds periods of inactivity alternating with three 21-seconds periods of movements so that the duration of the total data collection was 126 seconds. The beginning and the end of each activation period were signaled with "go" and "stop" commands that were transmitted via headphones. During the activation periods, subjects moved their tongue horizontally inside the mouth at a previously practiced self-paced rate of approximately 0.5 Hz. During the period of inactivity, the tongue was resting in the middle of the mouth. The task was practiced prior to scanning session under the supervision of the experimenter to make certain that all subjects would correctly perform the task. During the scanning session, subjects kept their mouth and eyes closed at all times and were instructed to avoid eye movements.

3.1.3.3. Data acquisition and analyses

Blood oxygenation level dependent (BOLD) fMRI was carried out on a 1.5 T MR scanner (Philips Intera, Best, The Netherlands) using a single-shot, gradient-echo, echo-planar imaging (GE-EPI) sequence (TR/TE 3000ms/55ms, flip angle 90°). For each of 42 time points, 30 contiguous, axial slices (resolution 3.4x3.4 mm in plane with 5 mm slice thickness) covering the entire brain were acquired. The first two time points were discarded to eliminate T1 effects.

All fMRI data were processed and analyzed using statistical parametric mapping (SPM99, URL://www.fil.ion.ucl.ac.uk/spm). The scans of each subject were realigned intra-individually to the first image of the session to correct for head movements. The realigned pictures were then smoothed with a 10 mm gaussian kernel. Initially, the data were not normalized in order to preserve individual anatomical structures when comparing the size and signal intensity changes of regions activated by the motor task. The data were temporal band pass filtered (high cut off 0.012Hz, low cut off 0.25Hz) and scaled to the global mean. A general linear model was set up for each individual and linear contrasts were applied according to Friston and colleagues (Friston et al., 1995) to compare brain activation levels for the various task and rest conditions. Areas with statistically significant changes in signal intensity were determined by t-statistics on a voxel-by-voxel basis. Relying on cluster inference (Friston et al., 1994), clusters of neighbouring voxels were identified as significantly activated if they passed a threshold of $p<0.05$ (corrected for multiple comparisons). The resulting statistical parametric maps (SPMs) were used to derive further dependent variables.

Based on our own experience and other previous reports, horizontal tongue movements were expected to elicit bilateral activation cluster covering S1/M1 with the COG of each cluster mainly being located in the precentral gyrus (Alkadhi et al., 2002; Curt et al., 2002; Hesselmann et al., 2004). To quantify size and intensity of the activated areas in S1/M1 during tongue movement, we determined the number of voxels (nVox) and the maximum t-value (tVox) within the most prominent (highest t-Value) cluster including the inferior and lateral segment of the central sulcus.

To compare the individual location of the activated clusters, a further analysis was performed on the anatomically normalized data. Normalization was done according to the nonlinear, nonlabel-based approach proposed by Ashburner and Friston (1999), which transforms individually oriented images into a comparable frame of reference (MNI-Space) and reduces inter-individual anatomical variability so that remaining differences in cluster location may be attributed to shifted functional representation. With this analysis, the centres of gravity (COGs) of the activated clusters in S1/M1 were determined for each individual separately. To compute the COGs, coordinate vectors of each activated voxel were weighted with their t-values and the resulting sum vector of all coordinates was divided by the sum of t-values. COGs are represented in [x,y,z] coordinates and all three aspects are assessed independently to derive measures of location in the medial-lateral, superior-inferior, and anterior-posterior axis.

3.1.3.4. Quantitative and statistical analysis of activated regions

In a first step, we tested the reliability and reproducibility of the fMRI method by applying the one sample t-test together with the corresponding 95% confidence interval

(95%CI) to the differences between the measured parameters (i.e. number, intensity and location of the activated voxels of the cluster covering S1/M1) of the first and the second imaging session. Parametric techniques could be applied as no departures from the approximate normality assumption were found. As no significant differences in the relevant activation parameters were detected between the two sessions, only data from the first session were taken for further analysis. This kept the amount of data comparable between the control and amelic group.

In a second step, the number, intensity and location (COG) of the significantly activated voxels in S1/M1 in each hemisphere were analysed for the control group and the amelic group separately, and subsequently, the two groups were compared. Defined as the motor dominant hemisphere (hereafter referred to as "dominant hemisphere") was the left hemisphere in the right-handed control participants and the hemisphere controlling the sole, normally developed hand in the amelic subjects. The other hemisphere, namely the right hemisphere in the control participants and the hemisphere contralateral to the missing limb in the amelic subjects, was assumed to be the motor non-dominant hemisphere (hereafter "non-dominant hemisphere"). Statistical tests were first performed to check for hemispheric differences in activation size, intensity and location of the sensorimotor tongue representation in each group separately (Wilcoxon signed rank test). In a second step, dominant and non-dominant hemispheres of the amelic subjects were compared to those of the control participants (Mann-Whitney U test). Due to the relatively small number of subjects in the investigated groups, nonparametric analyses were conducted for the above-mentioned statistics. The corresponding 95%CI to all calculated differences was computed.

3.1.4. Results

3.1.4.1. Reliability and reproducibility of the tongue representation in the control group with normally developed limbs

The reliability and the reproducibility of the anatomical localization of the tongue representation were assessed by calculating the differences between the number, intensity and location of the activated voxels of the first and the second imaging session.

No statistically significant differences were found between the two imaging sessions with respect to the location of the COGs, as well as the number and intensity of the activated voxels. The mean differences with corresponding p-values and 95%CIs are listed in Table 3. Listed are means with the corresponding p-values and the range indicated by upper and lower 95% CI.

Table 3. Measured activation parameters in the control group: mean differences between first and second scanning session

	Difference between first and second session, mean Value	p-Value	95% Lower	95% Upper
Number of activated voxels				
right hemisphere	18.00	0.47	-38.70	74.70
left hemisphere	9.42	0.71	-50.96	69.81
Intensity of activated voxels, t-value				
right hemisphere	-0.35	0.66	-2.25	1.55
left hemisphere	-0.86	0.19	-2.30	0.58
Location of centre of gravity				
(COG)	1.13	0.22	-0.90	3.15
x right hemisphere	-0.42	0.77	-3.84	2.98
y right hemisphere	-1.42	0.54	-6.79	3.9
z right hemisphere	-0.71	0.22	-1.99	0.56
x left hemisphere	0.71	0.05	0.01	1.41
y left hemisphere	-2.43	0.27	-7.34	2.49
z left hemisphere				

3.1.4.2. Quantitative estimation of the activated areas

The individual data of the amelic and the control subjects are listed in Table 4. All control and amelic participants showed significantly activated clusters in S1/M1 bilaterally during horizontal tongue movements.

The statistical group analysis of the normally limbed control subjects showed the expected bilateral activations in S1/M1, with significantly more voxels activated in the left (i.e. dominant) as compared to the right (i.e. non-dominant) hemisphere (Wilcoxon Z=2.3, p=0.02). The mean difference between the two hemispheres was 30.8 voxels, 95%CI (9.1,52.6). The intensity of activated voxels did not differ between the two hemispheres (Wilcoxon Z=0.18, p=0.86).

Table 4. Quantitative analysis of the volumes, maximum t-values, and centres of gravity coordinates of the motor tongue representation in amelic and control participants

Side of amelia	nVox DH	tVox DH t-values	nVox nDH	tVox nDH t-values	COG DH x	y	z	COG nDH x	y	z
Right	71 (RH)	6,30	39 (LH)	6,45	58	6	25	-35	-7	60
Right	358 (RH)	11,82	330 (LH)	11,56	59	-17	19	-52	-16	38
Right	351 (RH)	9,72	435 (LH)	8,36	58	-2	16	-44	-15	44
Left	115 (LH)	7,57	196 (RH)	8,01	-54	-3	29	52	-7	39
Left	288 (LH)	14,07	328 (RH)	13,79	-48	-4	31	51	0	34
Left	174 (LH)	8,54	143 (RH)	9,60	-54	-7	35	58	-6	34
Left	68 (LH)	7,49	81 (RH)	7,76	-57	-3	16	60	-2	20
Left	123(LH)	7,26	251(RH)	9,20	-54	-7	32	53	-4	34
Mean	193.5	9,1	255.3	9,3	55.2*	-4.6	25.4	50.6*	-7.1	37.9
SD	121.3	2,6	139.9	2,3	3.6	6.4	7.5	7.9	5.7	11.3
No	48 (LH)	6,06	27 (RH)	5,84	-55	-2	28	62	7	17
No	259(LH)	9,41	274 (RH)	9,60	-54	-6	24	58	-7	23
No	39 (LH)	6,12	13 (RH)	5,69	-54	-8	24	58	-3	25
No	140 (LH)	10,72	74 (RH)	7,62	-55	-11	34	59	-4	23
No	215 (LH)	10,03	183 (RH)	11,08	-56	-2	23	63	-4	16
No	70 (LH)	6,26	9 (RH)	5,27	-56	3	26	61	1	25
No	121 (LH)	7,21	63 (RH)	6,71	-57	-6	19	60	-3	16
No	53 (LH)	5,98	58 (RH)	8,46	-57	-2	23	58	2	31
No	107(LH)	6,39	73 (RH)	6,96	-56	-10	29	58	-11	34
Mean	116.9	7,6	86.0	7,5	55.6*	-4.9	25.6	59.7*	-2.4	23.3
SD	77.1	1,9	87.4	1,9	1.1	1.9	4.3	1.9	5.2	6.4

nVox: number of significantly activated voxels, tVox: intensity of significantly activated voxels of the cluster covering S1/M1 in each individual subject's dominant and non-dominant hemisphere. COG: centre of gravity. RH: right hemisphere, LH: left hemisphere, DH: dominant hemisphere, nDH: non-dominant hemisphere.
Individual data and means with standard deviations for amelic and control participants.
* For the mean COGs in the amelic as well as in the control participants, the x coordinate is given in absolute numbers.

The amelic subjects showed task-related activation in the same S1/M1 regions as the control participants, but without any inter-hemispheric difference for number (Wilcoxon Z=1.2, p=0.20) and intensity (Wilcoxon Z=0.17, p=0.85) of activated voxels. Likewise, the separate analysis of the two subgroups, namely the group with the missing right hand and the group with the missing left hand, did not reveal any significant hemispheric difference for both number and intensity of activated voxels. The mean difference between the number of activated voxels in the dominant (left) and the non-dominant (right) hemisphere was -20 in the group with the missing left hand and -8 between the dominant (right) and non-dominant (left) hemisphere in the group with the missing right hand.

The comparisons between the groups (i.e. amelic group and control group) regarding the number and intensity of the activated voxels in S1/M1 revealed no differences between the dominant hemispheres (Mann-Whitney Z=1.5, p=0.12 for number, Z=1.6, p=0.10 for intensity). In contrast however, in comparison of the two groups' non-dominant hemispheres (i.e. the right hemisphere of the control participants and left hand missing subjects, and the left hemisphere of the right hand missing subjects) the amelic group showed a higher number of activated voxels than the control group (Mann-Whitney Z=2.3, p=0.02). The amelic group had a mean of 225 activated voxels, 95%CI (111,339) and the control group of 86, 95%CI (18,153) in the non-dominant hemisphere. No significant difference in voxel intensity was found between the two groups (Mann-Whitney Z=1.7, p=0.09).

3.1.4.3. Location of the activations in the control and amelic group

Figure 9 displays the locations of the individual COGs (rounded to the nearest voxel center) in S1/M1 for both hemispheres and all subjects. Table 3 lists the coordinates of each individual separately, as well as their means and standard deviations.

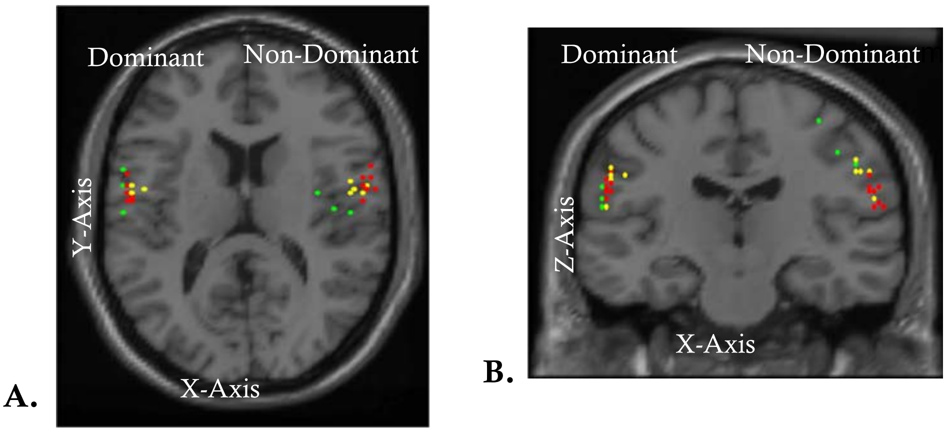

Figure 9. Displayed are the locations of the individual COGs of tongue movement activations after normalization. Green: participants with a right hand amelia (data are flipped left-right to group COGs with respect to dominant and non-dominant hemisphere, as explained in the text). Yellow: participants with a left hand amelia. Red: normally limbed control subjects. A: x, y coordinates projected onto a transverse section of a representative MNI standard brain through the most inferior COG. B: x, z coordinates projected onto a coronal section through the most anterior COG.

In the control group, the mean coordinates of the COGs in S1/M1 were x=-56, y=-5, z=26 in the dominant, left hemisphere and x=60, y=-2, z=23 in the non-dominant, right one. These COGs were significantly different in the x-coordinate (Wilcoxon Z=2.6, p<0.01), but not in the y- and z-coordinates. The difference of the COGs between the dominant and the non-dominant hemisphere for the x-coordinate was -4, 95%CI (-5.6,-2.5) indicating that the COG in the dominant hemisphere was located more medially than in the non-dominant one. The COG coordinates are located on the precentral gyrus, i.e. primary motor cortex and are quite similar to the ones previously published by our group (Alkadhi et al., 2002, Curt et al., 2002).

In the amelic group, the mean coordinates of the COGs in S1/M1 were x=55, y=-5, z=25 in the dominant and x=51, y=-7, z=38 in the non-dominant hemisphere. These COGs were significantly different for the z-coordinate (Wilcoxon Z=2.3, p=0.01), but not for the x- and y-coordinates. The mean difference between the dominant and the non-dominant hemisphere for the z-coordinate was -12, 95%CI (-23.6,-1.3) indicating that the tongue representation in the non-dominant hemisphere (contralateral to the missing limb) was located more superior than in the dominant one. The comparison between both amelic subgroups (i.e. with a missing right and a missing left hand) did not reveal any significant hemispheric difference in the location of the motor tongue COGs.

For the dominant hemispheres the comparison of the COGs' location in S1/M1 did not reveal any significant difference between control and amelic participants. In contrast, the location of the COGs in the non-dominant hemispheres differed significantly for the x-coordinate (Mann-Whitney Z=-2.8, p<0.01) and for the z-coordinate (Mann-Whitney Z=-2.7, p>0.01). In the amelic group the COGs were located significantly more medially (mean(x)=50.6, 95%CI (43.9,57.2)) and higher (mean(z)=37.9, 95%CI (28.4,47.3)) when compared to the control subjects (mean(x)= 59.7, 95%CI (58.1,61.1); mean(z)=23.3, 95%CI (18.4, 28.2)).

3.1.5. Discussion

The main findings of the present investigation can be summarized as follows: (1) normally limbed, right-handed subjects have a significant and reproducible left hemispheric dominance for horizontal tongue movements, (2) in the dominant, left hemisphere the activation in the S1/M1 is located more medially compared to the non-dominant, right hemisphere, (3) the amelic group does not show a hemispheric tongue dominance, and (4) the motor tongue representation in the non-dominant hemisphere of the amelic subjects is significantly enlarged and displaced cranially, when compared to the non-dominant hemisphere of the control subjects.

3.1.5.1. Reliability and reproducibility of activation in the control group

The data demonstrate the reliability and reproducibility of the imaging methodology and experimental protocol used for identifying location, intensity and spatial extent of areas activated by tongue movements. All participants were carefully instructed and supervised in the present research. They had practiced the tongue movements prior to scanning in order to secure a constant and reproducible performance of the task.

In a previous testing the reproducibility of brain activation patterns underlying body part movements, we had found the largest variability in the COGs of activated areas during movements of the tongue as compared to foot, elbow, wrist, and hand movements (Alkadhi et al., 2002). This variability may have been caused by the unrestricted and uncontrolled tongue movement performance in that study.

3.1.5.2. Hemispheric tongue dominance in subjects with normally developed limbs

The present study thus clearly confirms the left hemispheric dominance for tongue movements in normal-limbed, right-handed subjects. The horizontal tongue movements elicited a greater volume of activation in the left, dominant hemisphere in 78% of the right-handed control group members. Moreover, at the group level, a significant inter-hemispheric asymmetry was noted for the volume and location of the activation cluster in S1/M1. These results are consistent with other studies also reporting lateralized activation during non-speech related tongue movements, although in some of these studies, the lateralization was not statistically tested (Lotze et al., 2001; Hesselmann et al., 2004; Martin et al., 2004). Notably, some of the other groups, who did not report significant hemispheric differences in activation (Wildgruber et al., 1996;

Corfield et al., 1999), assumed a symmetrical motor tongue representation at least when the tongue movement was executed within a non-language related context.

As mentioned above, the differences in activation between the two hemispheres were found not only in the volume but also in the location of activated clusters. The COGs in the dominant hemisphere were located more medially than the COGs in the non-dominant one. According to the body representation in the motor cortex, the enlargement of the tongue area in a medial direction also implies a superior shift. A shift was also found in the z-axis but it did not reach statistical significance. These asymmetrical COGs contradict the previous reports describing the COGs of motor tongue representation as being highly symmetrical (Hesselmann et al., 2004) or the COGs in the right non-dominant hemisphere being located predominantly more superior (Martin et al., 2004).

There are few hypotheses concerning the existence of hemispheric lateralization of motor tongue function. The asymmetrical tongue representation may be explained by functional hemispheric differences in language processing (Picard and Olivier, 1983). The lateralization preference may also reflect an asymmetry in the activity of the articulatory muscles despite bilateral corticobulbar innervations (as suggested by Szirtes and Vaughan, 1977). Previous studies did not focus on the correlation between the degree of motor tongue lateralization and the degree of handedness. The potential relationship between hemispheric lateralization of language processing and asymmetries in cortical tongue representation has also not been covered in the literature to date. For addressing these issues, the cortical tongue representation in left-handers, as well as the motor tongue dominance in subjects with right-sided language dominance needs to be examined. Nevertheless, indirect conclusions concerning the relationship between handedness and tongue dominance can be drawn from studies on chewing side preference (Nissan et al., 2004). A relatively close relation between chewing side preference and handedness was found without any influence of peripheral dentine factors. In this study, the chewing side preference was defined as the side where a chewing gum is moved by the tongue for the first cycle of mastication. Thus, this measure appears to be a good indicator for behavioral tongue asymmetry, showing a link between handedness, behavioral and neurofunctional tongue dominance.

3.1.5.3. Absence of hemispheric tongue lateralization in amelic subjects

We investigated a potential alteration of the cortical sensorimotor tongue representation in the subjects born with a unilateral completely missing hand as compared to the normally limbed control participants. Specifically, we explored whether a shift or expansion of the motor tongue area into the deafferented hand area occurred in these amelic participants. In contrast to the strong lateralization of the motor tongue representation observed in the control participants, only 37.5% of the amelic subjects had a larger volume of activation in their dominant hemisphere as compared to their non-dominant one. The statistical group analysis revealed that both the activation volume and intensity did not differ between the two hemispheres, which lead to the conclusion that the amelic subjects do not show any hemispheric lateralization for the motor tongue representation. In addition to the lack of lateralization of the sensorimotor representation of the tongue in the amelic subjects, we have also found in a parallel study (unpublished data) that these subjects did not exhibit the expected hemispheric dominance pattern for linguistic processing. In a standardized tachistoscopic lexical decision task, we found left-hemispheric dominance for the language processing to be stronger in the subgroup of amelic subjects lacking a left hand than in a control group of 40 normally limbed, right-handed subjects. Thus, altered cortical representation of the tongue in response to absent hand motor activities may be accompanied by altered representations of higher-order cognitive tasks that are crucially dependent on tongue use, such as language. Interestingly, the lateralization of the motor tongue representation in the present study was not in the same direction as that of the language processing. We speculate that subjects with an absent left hand are very strong right-handers who simultaneously show strong left hemispheric language dominance as suggested by Knecht et al. (2000). Our results thus suggest that the degree of hand motor specialization correlates with the degree of language lateralization whereas the degree of tongue hemispheric dominance does not in a comparable way.

3.1.5.4. Shift of tongue representation in amelic subjects

Apart from the lack of a lateralized sensorimotor tongue representation, the second important finding in the amelic group was the clear superior shift of the COGs in the participants' non-dominant hemisphere. This finding received additional support by the comparison of the COGs in the amelic and the control group. Comparing the S1/M1 clusters in subjects' non-dominant hemispheres revealed a significant difference insofar as the COGs in the non-dominant hemisphere of the amelic subjects were larger and shifted in a medial and superior direction. These results demonstrate that the congenital absence of a limb is associated with alterations of the tongue representation in the hemisphere devoid of hand control. This alteration suggests a massive cortical reorganization involving enlargement and shifting of the sensorimotor tongue area towards the presumptive “hand“ area. Thus, cortical reorganization with the invasion of the never innervated hand area takes place in congenital "amputees" and not just in the previously reported traumatic amputees suffering from phantom pain (Montoya et al., 1998). It is possible that the reorganization of the normally developed but later deafferented sensorimotor cortex (as it is the case of the traumatic amputees) only takes place in conjunction with sensed phantom pain. Moreover, the present data suggest that early changes in the organization of the motor homunculus as in the case of congenital absent limbs can occur with or without concomitant phantom sensations in the respective limb.

3.2. Study 2: Motor processes in children's imagery: The case of mental rotation of hands

3.2.1. Abstract

In a mental rotation task, children 5 and 6 years of age and adults had to decide as quickly as possible if a photograph of a hand showed a left or a right limb hand. The visually presented hands were left and right hands in palm or in back view, presented in four different angles of rotation. Participants had to give their responses with their own hands either in a regular, palms-down posture or in an inverted, palms-up posture. For both children and adults, variation of the posture of their own hand had a significant effect. Reaction times were the longer the more awkward it would have been to bring their own hand into the position shown in the stimulus photograph. These results, together with other converging evidence, strongly suggest that young children's kinetic imagery is guided by motor processes, even more so than adults'.

3.2.2. Introduction

Several studies have shown that children as young as five years of age have kinetic imagery, that is, imagery representing movement (e.g., Marmor, 1975, 1977; Kosslyn, Margolis, Barrett, Goldknopf, & Daly, 1990). In earlier work, Piaget and Inhelder (1971) had claimed that this ability develops considerably later, only after children have entered the stage of concrete operations. Under seven years of age, according to Piaget and Inhelder's belief, children can have only static images. The question of what the properties of children's imagery are and when it develops has far-reaching implications for issues of cognitive development in general. If kinetic imagery actually plays a central role in children's thinking, then its properties will place major constraints on various cognitive processes that have been the focus of developmental research with young children. Outstanding examples, to name just two, are perspective taking abilities (e.g., Perner, 1991) and reasoning about the consequences of movement and object transformations in children's intuitive physics (e.g., Wilkening & Huber, 2002).

Young children's kinetic imagery abilities have been most clearly shown in variants of the mental rotation paradigm originally designed by Shepard and Metzler (1971) for studies with adults. In these experiments, pairs of relatively complex geometrical objects that were either identical or mirror images of each other were shown, and the task of the participants was to decide as fast as possible if the two objects were the same or not. What made the task difficult was that the two objects differed in their orientation in space, with varying degrees of angular disparity. The response times increased linearly with the size of the angle, suggesting that the participants had mentally rotated one of the two objects, until it was congruent with the other one. This result has since been replicated in many studies with adults (e.g., Kosslyn, 1994; Parsons et al., 1995; Shepard & Cooper, 1982) and with children of different ages (e.g., Kail, Pellegrino, & Carter, 1980; Levine, Huttenlocher, Taylor, & Langrock, 1999; Marmor, 1975; 1977). It should be noted that in most of the developmental experiments, the three-dimensional forms of the Shepard and Metzler paradigm were replaced by two-dimensional stimuli. In the seminal developmental study by Marmor (1975), for instance, children were shown drawings of panda bears in different orientations in the picture plane, and the task was to decide whether the two bears in each pair were the same or different.

In recent years, the research focus has shifted from simply demonstrating the existence of kinetic imagery to a deeper understanding of the nature of the phenomena. It appears that a host of processes is involved, and that mental rotation is less "mental" and more reliant on representations of one's own moving body than was previously conceived. In particular, mental rotation seems to be guided by motor processes, with the motor system being the engine driving the cognitive operations, rather than just the output system as which it is usually seen (Wexler, Kosslyn, & Berthoz, 1998). The most striking evidence for this view comes from experiments in which pictures of rotated human body parts such as hands had to be identified. Using modern neuroimaging techniques, Kosslyn, Digirolamo, Thompson, & Alpert (1998) showed that mental rotation of pictures of hands activated the primary motor cortex and associated higher-order motor areas, which was not the case in mental rotations of the geometric objects used by Shepard and Metzler.

Based on data like these, the authors proposed the existence of two distinct mechanisms in mental rotation: (a) an internal strategy, in which the person anticipates what she would see if she were to produce the rotation herself by a physical manipulation, and (b) an external strategy, in which the person attempts to visualize the consequences of a movement produced by some external force. In this view, only the internal mechanism recruits processes that prepare motor movements, while the external mechanism does not. The findings of Kosslyn et al. were largely corroborated, and partly elaborated, in several follow-up neuroscience studies (e.g., Kosslyn, Thompson, Wraga, & Alpert, 2001; Thayer, Johnson, Corballis, & Hamm, 2001; Vingerhoets, de Lange, Vandemaele, Deblaere, & Achten, 2002). Ganis, Keenan, Kosslyn, and Pascual-Leone (2000) took the line of reasoning one step further, by showing that disruption of primary motor cortex functioning by transcranial magnetic stimulation (TMS) slowed down the speed of mental rotation of pictures of hands, a result strongly suggesting that motor processes may even play a causal role.

The conclusions drawn from recent neuroimaging data are in accordance with behavioral data that had been obtained in earlier work (e.g., Sekiyama, 1982). Most notable is a study by Parsons (1994), in which adult participants had to decide whether a picture showed a left or a right hand, the hands being portrayed in palm or back view in different orientation in space. Reaction times (RTs) depended strongly on the awkwardness of the movement the participants would have to perform physically to rotate their own hand into the depicted position. By varying the position of the participants' hands during the experiment, Parsons could show that the spatial origin from which the simulated action started was as decisive a factor as was the "canonical" view of the pictured hand.

The idea of a canonical orientation had been put forward by Cooper and Shepard (1975) in their seminal experiment on laterality decisions of visually presented hands ("a left or a right hand?"). Their participants showed a clear reaction time (RT) advantage for stimulus hands with the fingers pointing upward compared to downward. Cooper and Shepard discussed two possible reasons for this effect. First, they emphasized the fact that people see their own hands in a position with fingers down less often, and that the more canonical fingers-up view would therefore facilitate RTs. Second, referring to some of their subjects' introspective reports, they already considered postural-kinaesthetic constraints and referred to the "physical awkwardness of positioning one's own (right or left) hand in that inverted orientation" (p. 54). The notion of canonical visual representations favoring some stimulus hands over others was also discussed with respect to an advantage, in hand laterality decision tasks, for back vs. palm views of hands. It was argued (e.g., Ashton, McFarland, Walsh, & White, 1978) that this advantage arises from a more frequent visual exposure to one's own backs of hands than palms. An alternative explanation, however, would be that participants in experiments like those mentioned here regularly hold their hands in a palms-down posture while performing the RT task. RTs to backs of hands might thus be faster because this stimulus does not require any kinaesthetic imagery of a hand rotation around the wrist.

Surprisingly, there are virtually no developmental data contributing to the debate on the relative importance of visual vs. kinaesthetic canonical representations for successful performance in tasks requiring the mental rotation of body parts. Such data may shed additional light on some important issues in the field. For instance, if the effect of past visual experience (i.e., the canonical view effect) were a primary factor, one should not expect a stronger effect in young children, because it is implausible to assume that in their visual experience the advantage for finger-up or back hand views would be greater compared to adults. In contrast, if motor-kinaesthetic factors were more decisive, one would predict stronger effects in young children because, according to the prevalent view, sensorimotor and visual processes are more tightly coupled than at older ages (Bertenthal & Clifton, 1998; Piaget, 1954; Rosenbaum, Carlson, & Gilmore, 2001). In any case, it seems desirable to back up the current discussion with developmental data from children in the age that has been of interest in other research on mental rotation and to extend the hand rotation task to children. The present experiment is a first attempt in this direction.

To further investigate the coupling of sensorimotor and visual processes, we introduced a variation of the hand posture. During the experiment, children and adults held their own hands either with their palms down (i.e., backs up) or palms up (i.e., backs down). In accordance with the existing literature, we predicted a clear advantage for judging back views over judging palm views when the own hand is in the regular palm-down posture. Specifically, for the novel variation introduced in this experiment, we expected a reduction of the back-view advantage when the own hand has the opposite posture during responding, that is, palm up. Of particular interest was the question if this effect, if it should occur at all, would be smaller or larger for children than for adults. If it turned out to be larger, this could be taken as an indication of the fact that for children, in particular, the posture of the own hand plays an important role when judging visually presented hands and, thus, would provide strong support for the view that their kinetic images are tightly coupled to and even may be guided by motor processes.

3.2.3. Preliminary Study

In a preliminary study, we wanted to make sure that the children who should take part in the main experiment were able to (a) make left-right discriminations and (b) perform mental rotations of pictures of objects other than parts of the human body.

3.2.3.1. Method

3.2.3.1.1. Participants.

Participants were 22 children (11 boys and 11 girls) from two kindergarten classes in Zurich, Switzerland. Age ranged from 5 years 5 months to 7 years 2 months; the mean age was 6.6 years (SD=0.6 years).

3.2.3.1.2. Materials.

Stimuli were 24 (3 x 4 x 2) drawings of cars, including three different types of cars, each in four angles of rotation, 0°, 90°, 180°, or 270° along the vertical axis, and in two driving directions, facing to the left or to the right in the unrotated position of 0° (see Figure 10 for three sample stimuli). The stimuli were presented on a portable Macintosh computer in the centre of the monitor. They extended a visual angle of maximally 12° both horizontally and vertically. Responses were given via two buttons fixed on a wooden keyboard that lay on the table in front of the Laptop, the two buttons being 32 cm apart.

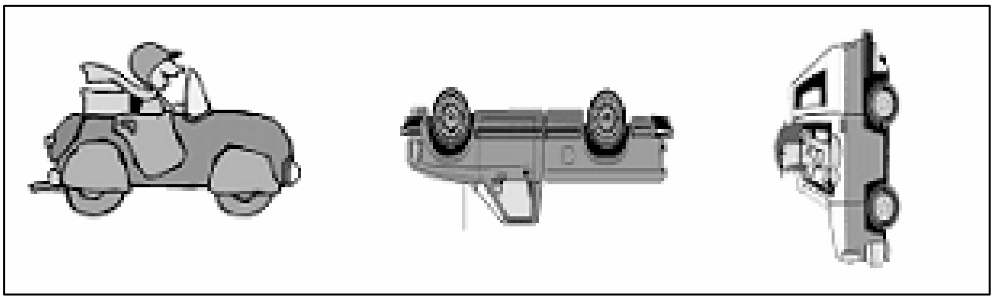

Figure 10. Three sample stimuli out of the set of 24 stimuli used in the preliminary study. Shown are cars in a 0°, 180° and 270° orientation, from left to right.

3.2.3.1.3. Procedure

The children's task was to find out whether the presented car would drive to the left or to the right. Obviously, cars that were not in a horizontal position had to be (mentally) rotated for that purpose. Children were told that if they concluded that the car's driving direction was to the right, they should press with their right hand the right button, and if they concluded that the driving direction was to the left, press with their left hand the left button. Each child judged the 24 stimuli in three different random orders. Children were encouraged to give their decisions as fast and as correct as possible. Stimulus exposure was terminated by the child's pressing of the button (left or right).

3.2.3.2. Results and discussion

The chance level of correct responses in the present task was 36, half of the total of 72 possible. Individual performance was significantly above chance level if the number of correct responses was 45 or more, $p < .05$. This was the case for 20 out of the 22 children. The two children who failed to reach the criterion, one boy and one girl, gave 43 and 41 correct responses, respectively. Their data were discarded from further analyses. For the remaining 20 children, the percentage of correct responses was 99%, 94%, 65%, and 94%, for the rotation angles of 0°, 90°, 180°, and 270°, respectively.

A three-way repeated measures ANOVA of the RTs of correct responses (with gender as between-subject factor and rotation angle and left-right orientation as within-subject factors) yielded, as expected, a significant main effect for rotation angle, $F(3, 54) = 44.06$, $p < .01$, reflecting a significant increase in RTs with the increase of the rotation angle of the stimulus to be judged from the standard orientation of 0° or 360°. RTs were significantly different from one another for all pairs of rotation angles, $ts(19) > 4.77$, $p < .01$, except for those of 90° and 270°, $t(19) < 1$. No other main effects or interactions were significant.

The results of this preliminary study clearly show that children in kindergarten age can use mental rotation in making left-right decisions about two-dimensional objects. In view of evidence from previous studies indicating that mental rotation abilities undergo a strong development around the age of 5 to 6 years, it is interesting to note that those two children who failed to reach the criterion were the two youngest participants in this study, both 5-year-olds. All other children were found to have the basic qualifications for participation in the main experiment.

3.2.4. Main experiment

3.2.4.1. Method

3.2.4.1.1. Participants

Those 20 children who had performed above chance level in the preliminary study participated in the main experiment. Of those, 5 girls and 3 boys were excluded from main data analyses because their performance did not exceed the chance level in this experiment (see below). Data will thus be reported for the remaining 12 children, 5 girls with a mean age of 6.7 years (SD=0.5 years), and 7 boys with a mean age of 6.6 years (SD=0.6 years). All of these children showed a clear right hand preference according to performance-based criteria from the NEPSY test battery (Korkman, Kirk, & Kemp, 1998).

In addition to the children, 24 adults, 12 male and 12 female, participated in this main experiment. Age ranged from 20 to 40 years ($M = 31.74$, $SD = 8.32$). Most adult participants were students or had already received an academic degree, all 24 were right handed, assessed by procedures suggested by Chapman and Chapman (1987).

3.2.4.1.2. Materials

Stimuli were 16 (2 x 2 x 4) photographs of human hands, left and right hands, each with palm or back view, that is, with a rotation along the longitudinal axis of the arm, each in four different rotation angles along the perpendicular axis of the arm, 0°, 90°, 180°, or 270° (see Figure 11). The photographs were presented on a portable Macintosh computer in the centre of the monitor. Maximal horizontal and vertical extension was 12° of visual angle, as for the cars in the preliminary study. Responses for left-right decisions were given via the same keyboard used in the preliminary experiment. For the inverted response condition introduced here (palms up), the keyboard could be turned upside down.

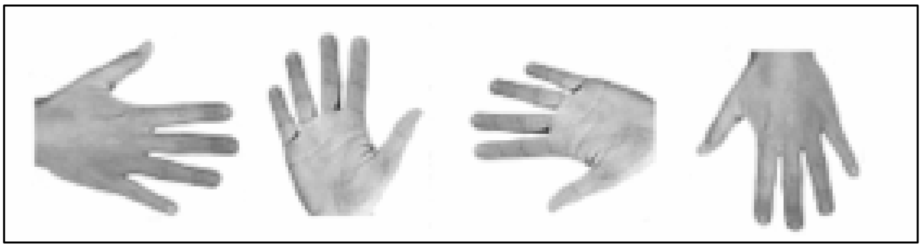

Figure 11. Four sample stimuli out of the set of 16 different stimuli used in the main experiment, with palm or back views of a left or a right hand in four degrees of rotation, 90°, 0°, 270° and 180°, from left to right.

3.2.4.1.3. Procedure

Participants had to decide as fast and correctly as possible whether the presented hand was a right or a left one. Left-right decisions had to be given by pressing a left or a right response key on the ipsilateral side of the keyboard. Stimulus exposure was terminated by the participant's pressing of the response key or by the exposure time limit of 7000 ms for the children and 3000 ms for the adults. In each response condition, the 16 stimuli were presented in three different random orders for the children and in four different random orders for the adults. In one response condition, the key had to be pressed in a regular hand posture, that is, palms down. In the other response condition, the key had to be pressed upward in an inverted posture, that is, palms up, under the same keyboard. In both conditions, participants' hands and underarms were covered by a cloth to prevent the view of the own limbs (see Figure 12). Presentation order of the two response conditions was counterbalanced in both age groups.

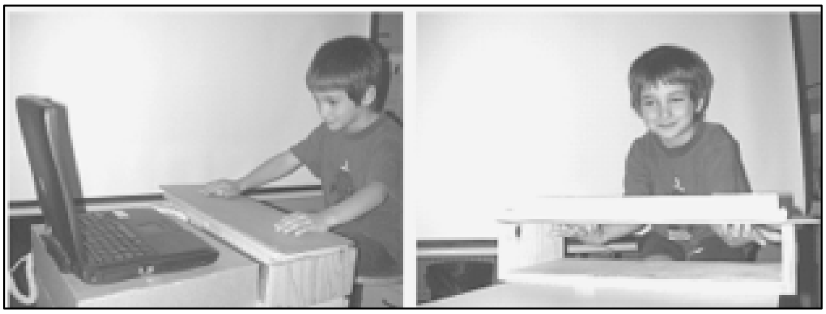

Figure 12. A child performing the task with a regular, palms-down posture (left side) and with an inverted, palms-up response posture (right side). Note: The cloth that covered participants' hands in both response conditions is not shown here; their hands were totally invisible to them while responding.

3.2.4.2. Results

Children

For children, chance level of correct responses was 48, half of the total of 96 stimulus presentations. Individual performance was significantly above chance level when the number of correct responses was 58 or more, $p < .05$. This was the case for 12 out of the 20 children. The data of those 8 children who did not reach the criterion were discarded from further analyses.

A five-way repeated measures ANOVA of the RTs of the 12 children's correct responses[10], with gender as a between-subjects factor and stimulus laterality, palm-back view, rotation angle, and response posture as within-subjects factors, revealed a significant main effect of rotation angle, $F(3, 30) = 9.50$, $p < .01$, in line with the pattern to be expected for mental rotation. With increasing distance of the rotation angle from the 0° or the 360° orientation, respectively, mean RTs increased. They were significantly different from one another for all pairs of angles, $ts(11) > 2.42$, $p < .05$, except for the 90°-270° pair, both rotations with fingers in horizontal orientation, $t(11) < 1$.

Significant interactions were found between (a) stimulus laterality and palm-back view, $F(1, 10) = 8.94$, $p < .05$, (b) palm-back view and rotation angle, $F(3, 30) = 5.08$,

[10] RTs of correct responses correlated negatively, $r = -.22$, $p < .01$, with accuracy, measured via number of correct decisions. That is, correctness of decisions was associated with faster rather than slower responses. Thus, the RTs presented here do not reflect a speed-accuracy tradeoff – a finding that further strengthens the analyses based on RTs.

$p < .01$, and (c) stimulus laterality and rotation angle, $F(3, 30) = 6.16$, $p < .01$. These interactions reflected (a) faster responses for back compared to palm views for right hands, $t(11) = 3.38$, $p < .01$, but not for left hands, $t(11) < 1$, (b) faster responses for back views at 90°, for palm views at 180°, and no RT advantage of back or palm view at 0° and 270°, and (c) faster responses for left hands at 90°, $t(11) = 2.96$, $p < .05$, but for right hands at 270°, $t(11) = 2.31$, $p < .05$, whereas there was no RT advantage of either hand at 0° and 180°.

Crucially, there was also a significant interaction of palm-back view and response posture, $F(1, 10) = 17.58$, $p < .01$. While back views of pictures of hands were recognized significantly faster than palm views when the own hand was in the regular, backs-up response posture, $t(11) = 4.95$, $p < .01$, this was not the case for the inverted response posture. In fact, when children responded with their palms up, there was a numerically, even if statistically not significant RT advantage for recognizing pictures of palms (see Figure 13, left panel).

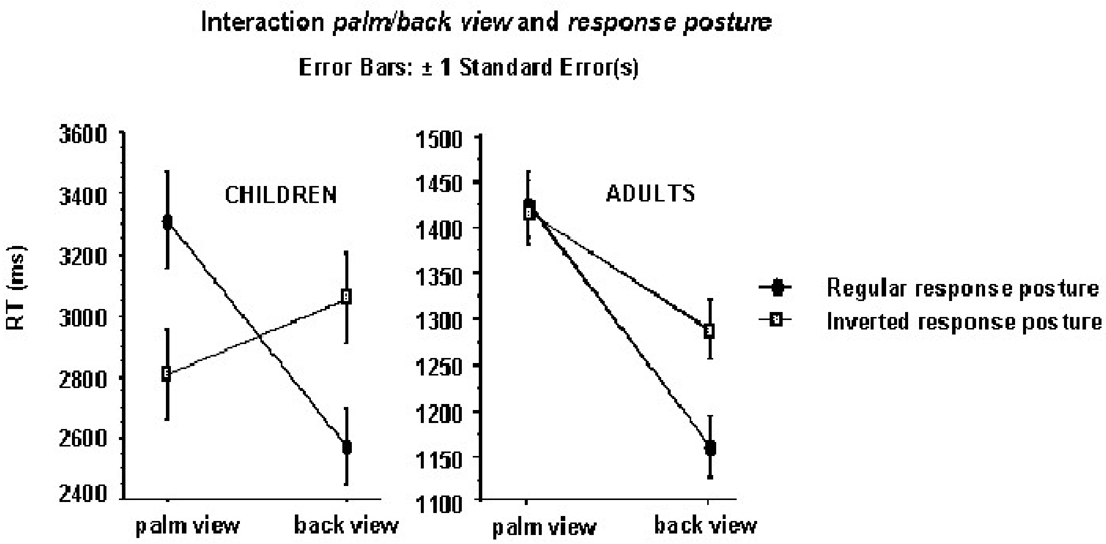

Figure 13. Mean RTs of children (left panel) and adults (right panel) for visually presented hands in palm or back view in the two response conditions: regular and inverted posture of own hands.

Adults

All adults performed above chance level as to their left-right decisions on the individual level. The analogous ANOVA of their RTs for correct responses yielded three significant main effects: Pictures of backs were faster recognized than pictures of palms, $F(1, 22) = 17.62$, $p < .01$, pictures of right hands were faster recognized than pictures of left hands, $F(1, 22) = 36.03$, $p < .01$, and RTs increased with an increasing distance in rotation angle from the unrotated, fingers-up orientation of the hand, $F(3, 66) = 45.53$, $p < .01$, according to the pattern to be expected for mental rotation: Mean RTs were significantly different from one another for all pairs of rotation angles, $ts(23) > 3.55$, $p < .01$, except for the 90°-270° pair, $t(23) < 1$.

In addition to the three significant main effects, three significant two-way interactions were found: First, there was a significant interaction of palm-back view and rotation angle, $F(3, 66) = 6.56$, $p < .01$, reflecting the fact that backs were significantly faster recognized than palms at rotation angles of 0°, 90°, and 270°, $ts (23) > 3.79$, $p < .01$ but not at 180°, $t < 1$. Second, there was a significant interaction of stimulus laterality and rotation angle, $F(3, 66) = 15.03$, $p < .01$, due to faster RTs for right hands at rotation angles of 0°, 180°, and 270°, $ts(23) > 2.90$, $p < .01$, and for left hands at 90°, $t(23) = 2.99$, $p < .01$.

Third and most importantly, there was a significant interaction of palm-back view and response posture, $F(1, 22) = 7.50$, $p < .01$. Although the adults responded to back views significantly faster than to palm views in both posture conditions of the own hand, $t(23) = 5.30$, $p < .01$ for the regular, backs-up condition and $t(23) = 2.30$, $p < .05$ for the inverted, palms-up condition, the postural manipulation significantly reduced the back view advantage, $t(23) = 2.30$, $p < .01$. In other words, when adults could hold their own hands in palms-up posture, they recognized palm-view pictures of rotated hands virtually as fast as in the regular backs-up posture, whereas for the back-view pictures they were clearly slower when they held their own hands in the inverted palms-up posture (see Figure 13, right panel). This interaction indicates that the time taken for mental rotation of visually presented hands is not independent from the momentary posture of the person's own hand.

3.2.5. General discussion

The present results replicate well-know findings from previous studies (e.g., Marmor, 1975; Kosslyn et a., 1990) showing that children by the age of six years of age have the ability to mentally rotate visually presented objects, which implies that their imagery is not just static, but also kinetic. This was clearly demonstrated in our preliminary study, in which the objects to be mentally rotated were pictures of cars, and also in the main experiment, in which the objects to be mentally rotated were pictures of hands. In addition to what is already known from previous studies in the field, the present data show that children at kindergarten age can not only mentally rotate when they have to recognize the sameness, that is, the congruence of visually presented objects but also when they have to make left-right decisions about them.

Because, in the main experiment, unlike as in the previous developmental studies on kinetic imagery, we used pictures of parts of the human body as stimuli to be rotated, we could investigate whether and how children's mental rotation and thus their kinetic imagery is guided by motor processes. For this purpose, we introduced a novel variation of the task: During the experiment, the children (as well as the adults) held their own hands either in the regular, palms-down or in the inverted, palms-up posture. An interesting question, then, was if RTs for the visually presented hands, left and right ones in palm or back view, were particularly long when it would be difficult and physically awkward to bring the hand of the own body in that position. For example, for most people it is physically much more awkward to bring their right hand in palm view to a 90° position, fingers pointing to the right, than to a 270° position, fingers pointing to the left.

In the present data there are many indications for contributions of motor processes in children's kinetic imagery. Most compelling is the interaction of palm-back view of the visually presented hands and the posture of the own hand, which turned out to be significant for children and for adults. For children, the usual RT advantage for back views of hands was completely eliminated when they had their own hands in palms-up posture. In this condition, they correctly identified the pictures of left or right hands even faster when they were presented in palm view. For adults, the back-view advantage in RTs was still existent in the inverted, palms-up posture, although highly reduced. Thus, it may be concluded that the effect of the posture variation was even more remarkable for the children than for the adults. It is hard to find an explanation of this effect that would not in some way refer to children's implicit attempts to bring their own left or right hand – starting from its momentary posture – in the position that was presented in the visual stimulus. Recall that children could not see their own hands during all experimental trials.

There are several other pieces of supporting evidence, pointing to the contribution of motor processes: For instance, pictures of left hands were faster recognized in the 90° position, fingers pointing to the right, than in the 270° position, fingers pointing to the left, while the reverse was true for pictures of the right hand. Furthermore, pictures of hands that were in the same position as the child's own hand, that is, fingers up, were generally faster recognized than those of the same hands rotated by 180°, that is, fingers down. Although these two effects can, at least in principle, be explained via visual experience, referring to the fact that people see their own hands more often in the "canonical" fingers-up position (Cooper & Shepard, 1975), an explanation taking motor processes into account appears to be the more plausible one, particularly if these data are seen in combination with the unequivocal results on posture variation just discussed.

Besides contributing to the main question of the present experiment, the posture variation data obtained here can also be seen as relevant to the vast literature on mental rotation in adults. These data strongly suggest that the usual RT advantage for hands in back view is at least in part due to the postural bias present in conventional hand laterality tasks, and they emphasize the role of proprioception in the visual recognition of hands. Furthermore, the same data corroborate the view that adults' kinetic images are guided by motor processes, as discussed in the recent literature in cognitive psychology and neuroscience (e.g., Wexler et al., 1998; Vingerhoets et al., 2002).

In view of the present data, this point can be made even more strongly for children. For them, the effects indicative of motor processes were generally even higher than those found for adults. This is in line with the view that perceptual and sensorimotor processes are more tightly linked in young children than in adults, put forward and popularized by Piaget (1954). Also, our data are in accordance with a more modern version of this general view, the hypothesis that all intellectual skills – imagery included – are "performatory," that is that all skills are grounded in and supported by motor activity, even at high levels (Rosenbaum et al., 2001).

3.3. Study 3: Mental rotation of congenitally absent hands

3.3.1. Abstract

To investigate the impact of congenital absence of one or both hands on motor imagery we assessed hand laterality decisions in 14 participants with unilaterally and in 2 with bilaterally absent hands. In a control group with normally limbed participants we replicated the basic findings reported in the literature (influence of hand motor dominance and biomechanical joint constraints). Unilaterally amelic participants were slower to judge pictures of hands corresponding to the one they lacked. Yet, they showed joint constraints even for this hand. Among the bilaterally amelic participants, one with phantom sensations also showed similar constraints for both hands. Conversely, the amelic patient without phantom sensations was not influenced by motor system information. These results indicate that motor imagery of a hand never physically experienced is influenced by representations of its existing counterpart and suggest that a phenomenal experience of a body (phantom sensations) may constrain motor imagery as much a history of limb motor activity.

3.3.2. Introduction

Shepard and Metzler (1971) are generally considered pioneers in the experimental investigation of healthy subjects' ability to imagine objects in different degrees of rotation. They described what is thought to be at the heart of the laws of mental rotation, i.e. shortest reaction times (RTs) for objects to be imagined in a canonical, non-rotated view and a linear increase of RTs with increasing angular disparity to the upright orientation. It became soon apparent, however, that a certain class of stimuli would not obey this law. If the human body or parts of it form the target objects of mental rotation, processing times are no longer solely determined by visual mental imagery, but also by higher-order interactions between vision and bodily representations (Kosslyn, Digirolamo,Thompson, & Alpert, 1998; Parsons, 1994; Shenton, Schwoebel, & Coslett, 2004). That is, the evocation, in mental imagery, of a limb in a specific posture or spatial orientation, always requires a participation of the motor system; even if purely mental, any imagined rotation of a body part implies a covert simulation of the rotational movement.

One of the most frequently employed experimental paradigms in studies of the mental rotation of body parts is the hand laterality task (e.g., Parsons, 1987, 1994; Sekiyama, 1982). It requires laterality decisions to visually presented hands (mostly *open* palms and backs of left and right hands) in different orientations ("a left or a right hand?"). In this task, the mental chronometry of correct decisions clearly reflects the participation of the observers' motor system. First, right-handers recognize right hands faster than left hands, while left-handers do not show a comparably strong left-hand preference (Gentilucci, Daprati, & Gangitano, 1998). Second, backs of hands are faster classified than palms as long as the fingers are pointing up, but there is a palm-over back advantage for finger-down postures (Parsons, 1987). Third, hands whose fingers are pointing in a medial direction (i.e., towards the body's midsagittal plane) are faster responded to than those whose fingers are pointing laterally (i.e., away from the body's midsaggital plane; Parsons, 1994), a RT difference we henceforth designate the "medial-lateral gradient". All these observations illustrate that in recognizing static images of left and right hands in varying positions, observers implicitly move their own hands into the respective position in order to reach a laterality decision. The more awkward a displayed posture is the longer RTs will therefore be. This covert activation of the hand motor system in the visual inspection of hands was captured in several neuroimaging studies (e.g. Bonda, Petrides, Frey, & Evans, 1995; see Rizzolatti & Craighero, 2004, for the broader context) and immediately begs the question as to how task performance would be affected by different motor system lesions.

Table 5 summarizes neuropsychological studies investigating this question in different clinical populations. The stimuli in most of these studies were open right and left hands in a palm or back view and presented in different orientations (referred to, in Table 5, as "prototypical task"). Other studies included hands in different postures or with specific finger configurations. Table 5 does not include experiments in which hand postures were described verbally (e.g. Sirigu & Duhamel, 2001), or which required patients to pantomime an object use on grounds of pictured hands (Buxbaum, Sirigu, Schwartz, & Klatzky, 2003). Even if relevant to the broader context of mental rotation performance in patients with an impaired body representation, classics like Ratcliff (1979; see also Zacks, Michelon, Vettel, & Ojemann, 2004), which used whole body stimuli, are not included in Table 5. However, some of the investigators, whose reports are listed in Table 5, have also studied, apart from laterality decisions of hands, also those of feet and other lateral body parts.

Table 5. Synopsis of 17 studies using hand laterality tasks (visual presentation of hands in different orientations) with clinical populations.

Reference (chronological order)	Deficit of patient population	Notes to Stimuli and Procedure	Main findings
Dominey et al., 1995	asymmetrical (right side affected) Parkinson's disease, N=7	prototypical task	asymmetry favoring the left hand in real and imagined motor performance; longer RTs to right as compared to left hands
Coslett, 1998, Exp. 1	RH lesion with neglect N=3, without neglect N=3; LH lesion without neglect N=7	prototypical task	patients with neglect, but not those without identified pictures of left (contralesional) hands less reliably than pictures of right hands
Parsons et al., 1998	callosotomy patients, N=2	stimulus hands presented in right and left visual field	accurate judgments when handedness of stimulus contralateral to the hemisphere perceiving it, but inaccurate when ipsilateral
Brugger et al., 2000	bilateral limb amelia N=1	hand and foot postures in two orientations	accuracy and RT patterns as in normally limbed observers
Buxbaum et al., 2000, Study 7	ideomotor limb apraxia N=1	subject's hands in a position congruent or incongruent to that of the pictured hands	patient's performance (but not that of a control) more accurate in the congruent as compared to the incongruent condition
Rumiati et al., 2001, Exp.1, 2	left fronto-temporo- parietal damage, N=1	Exp. 1: prototypical task Exp. 2: different finger configurations	patient's performance in Exp 1. differed not from that of controls. Patient less accurate than controls in Exp. 2
Schwoebel et al., 2001	chronic unilateral arm pain, N=13	prototypical task	when presented under 180° longer RTs for stimuli representing the painful as compared to the unaffected arm
Johnson et al., 2002, Exp. 2	CVA with dense hemiplegia of the non dominant hand, N=8	prototypical task	more accurate judgments for contralesional than ipsilesional (hand) stimuli
Schwoebel et al., 2002	chronic unilateral arm pain, N=12	prototypical task	when presented under 180°, longer RTs to stimuli representing the painful compared to the unaffected arm (effect vanished after pain treatment)
Tomasino, Rumiati et al., 2003. Exp. 1, 2	apraxia with LH damage, N=1	Experiment 1: including hands, feet, eyes, arms etc. Experiment 2: different finger configurations	deficient performance as compared to controls for both experiments (Exp. 1, specifically for hands)

Table 5, contd.

Tomasino, Toraldo et al., 2003	unilateral brain lesion LH N=5, RH N=4	different finger configurations	only patients with LH lesions showed deficits in hand laterality judgments
Moseley, 2004a	complex regional pain syndrome of the wrist and/or hand N=18	different hand postures	longer RTs to stimuli depicting the affec ted hand. Response latency pain being related to symptom duration and to evoked by executing the real movement
Nico et al., 2004	upper limb amputees, N=16	prototypical task	longer RTs and less accurate task performance, but same response pattern as controls. Amputation of dominant hand and everyday use of prosthesis complicates laterality judgments
	congenitally absent hand, N=3		overall longer RTs than controls. Moreover, longer RTs to stimuli presented in awkward positions when stimulus corresponds to existing hand but not to the missing hand
	lesion of brachial plexus, right N=1, left N=1		small proportion of correct responses especially for stimuli depicting the affected limb in awkward positions
Schwoebel & Coslett, 2005	stroke patients, LH N=45, RH N=25	prototypical task	same performance in judging ipsilesional and contralesional hand stimuli
Tomasino et al. 2005	right brachial plexus lesion; N=1 electrode grid implanted over left primary motor cortex	patient instructed to use motor or visual imagery during motor cortex stimulation	cortical stimulation slows down performance under motor, but not under visual imagery condition
De Vignemont et al., 2006	schizophrenic patients N=13	prototypical task, but including fist/grasp	same performance pattern as controls but significantly slower and less accurate
Fiorio et al., 2006	right hand writer's cramp N=15	prototypical task, but including feet	overall longer RTs in judging hands but not feet. Same response pattern as controls

Abbreviations: CVA: cerebral vascular accident, LH: left hemisphere, RH: right hemisphere

Unilateral sensorimotor cortex lesions do not appear to have a homogenous effect on a patient's hand laterality performance. While Coslett (1998) reported that patients with neglect have deficits in recognizing exclusively the contralesional hand, Schwoebel and Coslett (2005) demonstrated symmetrical deficits in the recognition of ipsi- and contralesional hands. A similar symptom-specific dichotomy was described for patients with basal ganglia dysfunction. Specifically, patients with asymmetrical Parkinson's disease were slowed in classifying stimuli corresponding to their affected hand (Dominey, Decety, Broussolle, Chazot, & Jeannerod, 1995), whereas patients with focal hand dystonia showed a general slowing for stimuli corresponding to both their affected and unaffected hand (though not for feet; Fiorio, Tinazzi, & Aglioti, 2006). The work by Tomasino, Toraldo, and Rumiati (2003) uncovered a double-dissociation between the site of a hemispheric lesion and a patient's ability to rotate body parts and objects. While patients with left hemisphere lesions were impaired in the mental imagery of body parts (as revealed by a performance deficit in a hand laterality decision task) but not of objects, the converse was true for patients with right hemisphere damage. Further findings of the same research group revealed that apraxia due to left hemisphere lesions appears to be particularly impaired for the mental imagery of hands with non-prototypical finger positions (Tomasino, Rumiati, & Umilta, 2003). Hand laterality tasks have also been used to investigate the influence of pain on the body schema (e.g. Schwoebel, Friedman, Duda, & Coslett, 2001; Schwoebel, Coslett, Bradt, Friedman, & Dileo, 2002). It seems as if acute (experimentally induced) and chronic pain in the region of the lower arm and hand would have fundamentally different effects on a patient's task performance. While the latter prolongs RTs to stimuli specifically depicting the affected hand (Moseley, 2004a), the former rather delays those to the *non-affected* hand (Moseley, Sim, Henry, & Souvlis, 2005). One interpretation is that acute pain applied to the hand captures an observer's focal attention, thus disfavoring RTs to the other hand. Conversely, chronic hand pain appears to alter the central representation of the affected hand (Schwoebel et al., 2001). For the use of hand laterality tasks as a therapeutic tool in patients with complex regional pain syndrome see Moseley (2004b).

A study of Parsons and collaborators (Parsons, Gabrieli, Phelps, & Gazzaniga, 1998) is also included in Table 5, even though hand stimuli were not presented in the center of the visual field (as in all other work cited in Table 5), but lateralized to the left or right of a central fixation dot. Requiring two callosotomy patients to provide laterality decisions to these peripheral hand pictures, the authors could elegantly show that each hemisphere is capable to correctly classify "its own hand", but is at chance for laterality decisions of the ipsilateral hand.

Two studies from Table 5 are particularly relevant to the context of the present paper. First, Brugger and co-workers assessed hand (and foot) laterality decisions of a woman born without hands and feet (Brugger, Kollias, Müri, Crelier, Hepp-Reymond, & Regard, 2000). From the fact that RTs were prolonged for body parts with fingers (toes) pointing down rather than up, the authors concluded that their subject had a normal cortical representation of hands and feet. Although this assumption appears supported by neuroimaging evidence presented in the same publication as well as by later behavioral testing (Funk, Shiffrar, & Brugger, 2005), we note that only stimuli rotated zero or 180 degrees have been employed in the original report (Brugger et al., 2000, their Table 5). As slower processing times for hands displayed 180° rotated could also be explained by referring to the (visually) canonical view of a 0° angle (e.g., Ashton, McFarland, Walsh, & White, 1978), the authors' conclusions do not seem to be strictly warranted. We here examined the participant's performance on a more sophisticated version of a hand laterality task. In particular, we used pictures of hands whose fingers pointed to the left or right of the display and thus allowed to quantify a potential medial-lateral gradient not to be accounted for by pure visual canonics. The second study that examined hand laterality decisions in people with missing upper limbs is the one by Nico and collaborators (Nico, Daprati, Rigal, Parsons, & Sirigu, 2004). These authors described increased RTs to pictured hands specifically matching an observers' lost limb (only cases of unilateral amputations were studied), especially if this had been the dominant one. A significant medial-lateral gradient could be demonstrated for both absent and present hand. Nico et al. (2004) also investigated three persons with a congenitally missing upper limb. In contrast to the finding in amputees, the medial-lateral gradient showed up exclusively for the subject's preserved hand. One limitation of the experiment by Nico et al. (2004) is the failure to inquire, in the three subjects born with only one limb, presence or absence of phantom sensations. Although only a minority of people with limb aplasia experience phantoms of the missing limb (Price, 2006, for an overview), phantom status needs to be assessed in the single individual, especially in an experiment on interactions between vision and body schema. Any behavioral data in Nico et al.'s (2004) congenital amputees can only be reasonably interpreted if such information were available. Already Sekiyama (1982; p. 95) recognized that "... it is conceivable that the mental representations generated in [hand laterality tasks] might share some properties in common with what is called 'phantom limb'". In fact, the participant in Brugger et al.'s (2000) and Funk, Shiffrar et al.'s (2005) experiments reported vivid phantom sensations of all missing limbs, and the authors emphasized that the behavioral, neuroimaging and neurophysiological evidence for spared cortical representations of hands must be interpreted in the light of this phenomenal awareness of limbs.

The current study aimed to further explore the mental rotation of congenitally absent hands. We wondered whether biomechanical constraints that had never been physically experienced nonetheless influenced an observer's hand laterality decisions. Specifically, in a group of people born with only one hand, we planned to investigate whether a medial-lateral gradient would be found for both hands or only for the preserved hand. We also carefully questioned each participant as to a possible history of phantom experiences and would have predicted stronger effects of joint constraints in the subjects with as compared to those without such a history. It may be anticipated here that not one single of the 14 participants tested had ever experienced any phantom limb phenomena, such as this prediction could not be tested. However, in addition to the subjects with unilateral hand amelia, we also examined two persons with bilaterally missing limbs (both cases of congenital amelia). Crucially, one did report very vivid phantom sensations while the other had never experienced any (cf. Funk, Shiffrar et al., 2005).

3.3.3. Materials and methods

3.3.3.1. Participants

Fourteen persons with one hand missing since birth (hereafter referred to a: "unilaterally amelic participants"), two persons with congenital absence of both hands (hereafter "bilaterally amelic participants") and 24 normally limbed control subjects took part in the current study that had been approved by the local Ethics Committee. Written informed consent was obtained by every subject. No participant had ever suffered from serious health problems or developmental disorders as assessed by a standardized inventory (Campbell, 2000), and none had taken any medication affecting the central nervous system for at least the previous two weeks. All subjects scored in the normal range in a paper-pencil test of mental object rotation (Thurstone & Thurstone, 1941/1962). Participants were recruited by flyers, personal contact or by a self-help group for amelic persons.

3.3.3.1.1. Unilaterally amelic participants

Nine unilaterally amelic participants (5 women) with an absent left hand (hereafter "absL"; age range 8 to 33 yr, mean=17.4, SD= 8.7) and five unilaterally amelic participants (2 women) with an absent right hand (hereafter "absR"; age range 12 to 27 yr, mean=20.6, SD= 5.7 yr) were examined. A hand was regarded as missing if all fingers were absent. Only one person had a wrist articulation. No member of the unilaterally amelic group had ever experienced any phantom sensations of the missing limb during waking life (Brugger & Regard, 1998). However, some had experienced themselves performing bimanual activities during sleep dreams. Six subjects of the absL group and 3 subjects of the absR group used a prosthesis on a more or less regular basis (in 4 and 1 cases, respectively, this was of a mere cosmetic type and in the other cases of a myoelectrical type). The medical cause of the amelia was unknown in every instance. Figure 14A displays a participant with a missing left hand performing the hand laterality task.

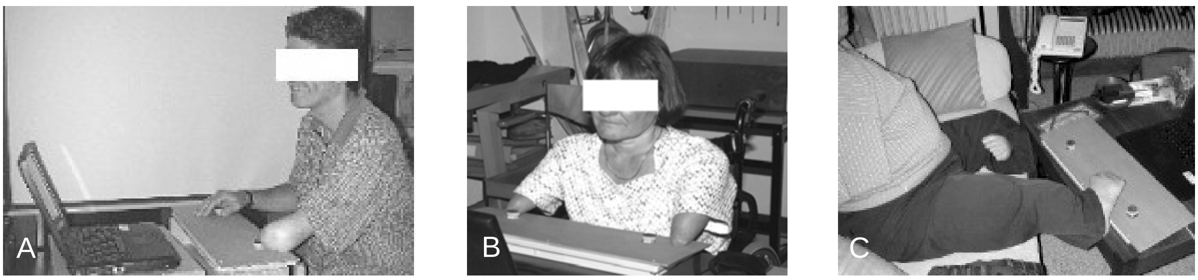

Figure 14. A participant with a unilateral missing left hand (panel A) and participant AZ with a tetra amelia (panel B) and CL with a bilateral hand amelia (panel C).

3.3.3.1.2. Bilaterally amelic participants

Two subjects with bilaterally missing hands participated in the present study. AZ is a university-educated woman, born 1953 without lower arms and lower legs. AZ experienced phantom sensations of her missing body parts as long as she can remember. CL is a journalist born 1962 without arms and shortened legs due to thalidomide-related embryopathy. In daily life, he uses his right foot for writing, eating, pointing, and gesturing. He has never experienced any phantom sensations of his missing limbs. More detail to these two participants' physical appearance can be found in Brugger et al. (2000), Brugger and Funk (in press) and Funk, Shiffrar et al. (2005). Figures 14B and 14C show them perform the hand laterality task.

3.3.3.1.3. Control participants

Twenty-four normally limbed adults, 12 men and 12 women, formed the control group for the amelic subjects. Their age ranged from 20 to 40 years (mean= 31.7 yrs., SD = 8.32 yrs). Most control participants were students or had already received an academic degree. All 24 members of the control group were right-handed according to the 13-item inventory of Chapman and Chapman (1987), and none had ever had a psychiatric or neurological illness nor suffered from developmental disorders (Campbell, 2000).

3.3.3.2. Preliminary experiment

The amelic subjects performed a preliminary experiment to ascertain that the physical attributes of their upper limbs (i.e. hand, stump or prosthesis) would not significantly impact manual responding. To this end, they were administered a mental rotation task with non-body related objects, i.e. cars, as stimuli. This task was previously used to assess children's mental object rotation performance (Funk, Wilkening, & Brugger, 2005).

3.3.3.2.1. Materials

Drawings of cars (50% driving to the right side, 50% driving to the left side, 4 angles of rotation 0°, 90°, 180° and 270°, clockwise along the vertical axis) were presented in the centre of the screen of a portable computer. All these stimuli extended maximally 11.4° of visual angle both horizontally and vertically. Stimulus presentation and response collection were controlled by SuperLab software Pro Version 2.0 (Cedrus Corporation, 2002).

3.3.3.2.2. Procedure

The task was to decide as fast and as correctly as possible the driving direction (left or right) of a car, or whether the presented car would drive to the left or to the right side if placed on the wheels (corresponding to a 0° rotation). "RIGHT" ("LEFT") decisions had to be provided by pressing a right-sided (left-sided) key on a 2-key special purpose keyboard with the right (left) hand, stump or prosthesis. CL used the same keyboard, but pressed the response keys with his right foot (initiating both left-sided and right-sided responses from a location in between the two keys; Figure 14C). The two response keys could be adjusted in height to be optimally comfortable for an individual subject. Participants responded to 72 randomized stimuli (3 repetitions of 24 different stimuli). Stimulus exposure was only terminated by the participant's response.

3.3.3.3. Main experiment: Hand laterality task

3.3.3.3.1. Materials and Procedure

Photographs of human hands (50% left and 50% right hands; 50% back views and 50% palm views; 4 angles of rotation: 0°, 90°, 180° and 270°, clockwise along the vertical axis) were presented on a portable computer in the centre of the screen. See Figure 15 for four sample hand stimuli. Maximal horizontal and vertical extension of a stimulus was 11.3° of visual angle, very similar to the cars presented in the preliminary experiment. Participants were required to decide as fast and correctly as possible whether a presented hand stimulus depicted a left or a right hand. Response keyboard and key assignments were identical to the preliminary experiment. Stimulus presentation and response collection were again controlled by SuperLab software Pro Version 2.0 (Cedrus Corporation, 2002).

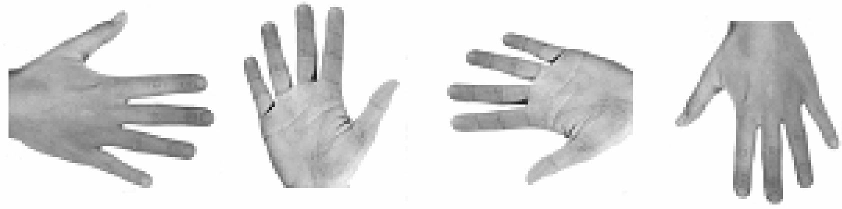

Figure 15. Four out of 16 stimulus samples used. Displayed are, from left to right angles of 90°, 0°, 270°, and 180°. 50% of the stimuli represented left hands, 50% right hands. Orthogonally, 50% of the hands were presented in palm view, 50% in back view.

3.3.3.3.2. Procedure

Normally limbed control participants and the unilaterally amelic participants responded to 64 randomized stimuli (4 repetitions of the 16 different stimuli). The two bilaterally amelic subjects responded to 160 randomized stimuli (10 repetitions of the 16 different stimuli).

Stimulus exposure was only terminated by the participants' response. During the task a dark cloth was covering hands and underarms (or prostheses, respectively) to prevent a visual image of the own limbs or limb-substitutes.

3.3.4. Results

All data of the preliminary study as well as the main experiment were transformed logarithmically due to their skewed distribution.

3.3.4.1. Preliminary Study

3.3.4.1.1. Unilaterally amelic participants

All participants performed above chance (i.e. >44 correct responses, corresponding to significantly more than 36 to be expected by chance; 5% alpha level). A four-way repeated measures ANOVA with the between-subjects factors *gender* and *side of missing limb* and the within-subject factors *driving direction (i.e. right or left)* and *angle of* *rotation* of the RTs of correct responses was calculated. There was a significant main effect for the factor *missing limb* ($F(1,10)=10.31$, $p<.01$), reflecting faster responses by absR than by absL subjects. There was also a significant main effect of *angle of rotation* ($F(3,30)=17.35$, $p<.001$); the more the displayed car was rotated away from 0° (both clockwise and counterclockwise), the longer was the corresponding RT. RTs to the cars displayed in the different angles of rotation were all significantly different from one another ($ts(13)>3.28$, $p<.01$), except those to cars presented in 90° or 270°, respectively, ($t(13)=.23$, $p=.81$).

Most important was the finding that the interaction between the factors *driving direction* and *missing limb* was clearly not significant ($F(1,10)=1.48$, $p=.25$), showing that RTs of responses with a stump or a prosthesis were not statistically different from those provided by a normally developed hand.

3.3.4.1.2. Bilaterally amelic participants

Separate ANOVAs of AZ's and CL's RTs of correct decisions (factors *driving direction* and *angle of rotation*) revealed a significant main effect for the factor *angle of rotation* for both AZ ($F(61,3)=29.06$, $p<.001$) and CL ($F(47,3)=12.86$, $p<.001$). Also for both participants, there were no significant differences between RTs to right driving and RTs to left driving cars. This ensures that AZ's upper arm stumps and CL's right foot would not show any motor bias for one or the other response key.

3.3.4.2. Main experiment: Hand laterality task

All participants performed above chance (i.e. >90 correct responses, corresponding to significantly more than 80 to be expected by chance for the subjects receiving 160 trials and > 40 correct responses with a chance baseline of 32 for the subjects receiving 64 trials, 5% alpha level in each case).

3.3.4.2.1. Normally limbed control participants

A four-way repeated measures ANOVA of the RTs of correct responses, with *gender* as a between-subjects factor and *stimulus laterality* (left or right hand), *view* (palm or back) and *angle of rotation* (0°, 90°, 180°, 270°) as within-subject factors revealed significant main effects for the factors *stimulus laterality* (F(1,20)=20.62, p<.001), *view* (F(1,20)=30.53, p<.001) and *angle of rotation* (F(3,60)=62.55, p<.001). Right hands were faster responded to than left hands (t(23)=6.37, p<.001) and backs of hands were recognized significantly faster than palms (t(23)=4.58, p<.001). RTs to hand stimuli increased with their rotation away from 0° (up to 180° clockwise and counterclockwise). All RTs to hand stimuli presented under different angles of rotation were significantly different from each other (ts(23)>3.61, p<.001), except the RTs to those under 90° and 270° (t(23)=.14, p=.89).

In addition to the significant main effects, two two-way interactions turned out to be significant. First, the interaction between the factors *view* and *angle of rotation* (F(3,60)=13.67, p<.001) indicated that backs of hands were significantly faster recognized than palms when presented in rotation angles of 0°, 90° and 270° clockwise (ts(23)>4.35, p<.001). In contrast, palms and backs of hands were equally fast responded to (t(23)=.11, p=.91) when presented with fingers pointing down (i.e. 180° rotation). Second, the interaction between the factors *stimulus laterality* and *angle of rotation* (F(3,60)=9.80, p<.001) indicated that RTs to right hand stimuli were significantly faster than those to left hand stimuli when the hands were displayed in angles of rotation of 0°, 180° and 270° clockwise (ts(23)>2.62, p<.01), whereas left hands were tendentially faster identified (t(23)=2.19, p<.05) when presented in a 90° clockwise rotation (see Figure 16)

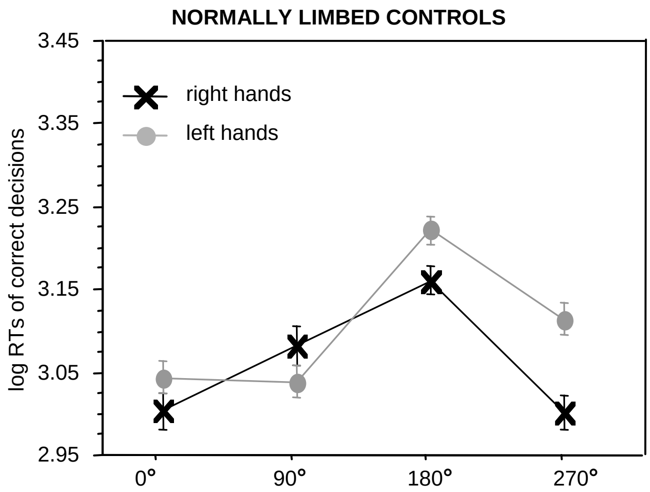

Figure 16. Significant interaction between *stimulus laterality* and *angle of rotation* in the participants of the normally limbed control group. Displayed are means ± standard errors.

RTs to right hand stimuli presented in angles of rotation of 0° and 270° clockwise were comparable (t(23)=.12, p=.90), but RTs to right hands displayed in all other angles of rotation differed significantly (ts(23)>3.23, p<.01) from each other. RTs to left hand stimuli presented in a angle of rotation of 0° or 90° clockwise (t(23)=.41, p=.68) were comparable, whereas the recognition of left hand stimuli displayed in all other angles of rotation differed significantly from each other.

Focusing on the medial-lateral gradient, we note that both right as well as left hand stimuli were significantly faster responded to when presented in a medial (i.e. 270° for right hands and 90° for left hands) as compared to a lateral orientation (i.e. 90° for right and 270° for left hands): right hands: t(23)=3.84, p<.001; left hands: t(23)=3.69, p<.001.

Finally, one three-way interaction was significant, namely the interaction between the factors *view*, *stimulus laterality* and *angle of rotation* (F(3,66)=3.97, p=.01). To further explore the significant triple interaction, two separate two way ANOVAs (*stimulus laterality* and *angle of rotation*) were performed, one each for backs of hands and for palms. Apart from the main effect of *angle of rotation* (p<.01, for both categories) these analyses revealed a main effect of *stimulus laterality* for backs of hands (F(1)=12.30, p<.001) and a significant interaction between *stimulus laterality* and *angle of rotation* for palms (F(3)=4.78, p<.01). Right backs of hands were significantly faster recognized than left ones, and RTs to backs of hands presented in every angle of rotation were different from each other, except when presented in 90° or 270°. Palms were significantly slower recognized when presented upside down (i.e. 180°) as compared to all other presentation angles of 0°, 90° and 270°.

3.3.4.2.2. Unilaterally amelic participants

A five-way repeated measures ANOVA of the RTs of correct responses (between-subjects factors *gender* and *side of missing limb*, within-subject factors *stimulus-laterality*, *view* and *angle of rotation*) revealed main effects for the factor *view* (F(1,10)=32.81, p<.001) and the factor *angle of rotation* (F(3,30)=40.98, p<.001). Backs of hands were significantly faster recognized than palms (t(13)= 6.67, p<.001), and the RTs increased with larger angular deviations of the hand stimuli away from 0° (i.e. fingers pointing up).

Moreover, the following three two-way interactions were significant. First, the interaction between the factors *stimulus laterality* and *side of the missing limb* ($F(1,10)=31.22$ $p<.001$) indicated that both subjects with a missing right and those with a missing left hand responded significantly faster to hand stimuli corresponding to their normally developed limb than to those corresponding to their missing limb (absL: $t(8)=4.47$ $p<.01$, absR: $t(4)=3.85$, $p=.01$). Second, the interaction between the factors *view* and *angle of rotation* ($F(3,30)=6.52$, $p<.01$) indicated that the RTs of palms and backs of hands increased significantly with an increasing angle of rotation of the hand stimuli away from 0°/360°. Despite the significant interaction, backs of hands were significantly faster recognized than palms under every single angle of rotation ($ts(13)>5.12$, $p<.01$). Third, the interaction between the factors *stimulus laterality* and *angle of rotation* ($F(3,30)=6.95$, $p=.001$) indicated that RTs to right hands differed from those to left hands only under angles of rotation of 90° ($t(13)=6.36$, $p<.001$; left-hand-advantage) and 270° ($t(13)=9.45$, $p<.001$; right-hand-advantage). RTs of both right ($ts(13)>7.77$, $p<.001$) and left hands ($t(13)>8.61$, $p<.001$) increased significantly with an increasing angle of rotation away from 0°/360° (see Figure 17).

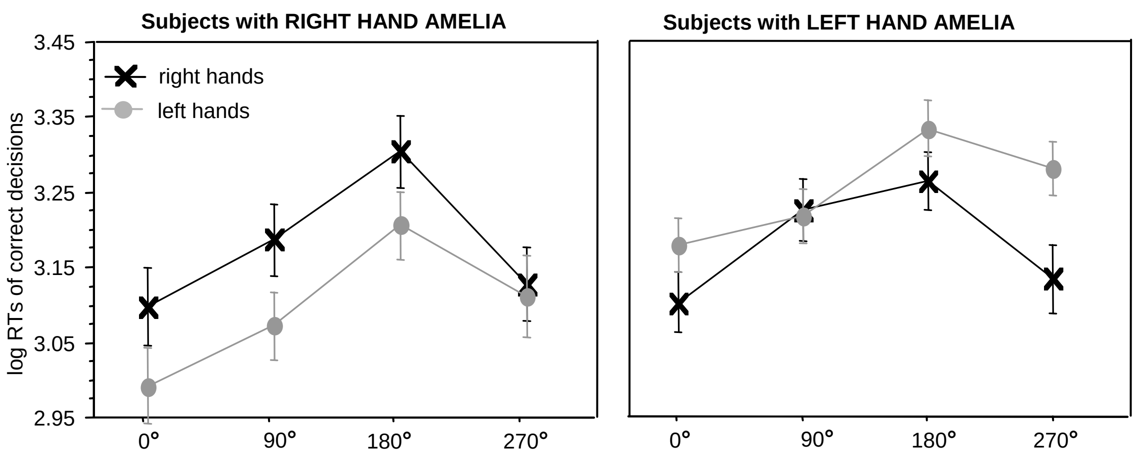

Figure 17. Significant interaction between *stimulus laterality* and *angle of rotation* in the participants with a unilateral hand amelia, the left panel displays the results of the participants with a missing right hand, the right panel the results of the participants with a missing left hand. Displayed are means ± standard errors.

Importantly, both groups showed a medial-lateral gradient for the preserved, but also for the missing hand (absR: right hands 90° vs. 270°: $t(4)=8.75$, $p<.01$, left hands 90° vs. 270°: $t(4)=3.62$, $p<.05$; absL: right hands 90° vs. 270°: $t(8)=12.96$, $p<.001$, left hands 90° vs. 270°: $t(8)=11.38$, $p<.001$).

Finally, one three-way interaction turned out to be significant, namely the interaction between *view, stimulus laterality* and *side of missing limb* $F(1,10)=5.86$, $p<.05$). To further explore this triple interaction, separate two-way ANOVAs (*view* and *stimulus laterality)* were performed for absL and absR participants separately. Both revealed main effects for *view* ($Fs(1)>9.21$ $p<.01$; back view advantage) and for *stimulus laterality* ($Fs(1)>5.33$ $p<.05$). The latter effect indicated that subjects of the absR group responded faster to left hand stimuli and vice versa, subjects of the absL group were faster to right hand stimuli.

3.3.4.2.3. Bilaterally amelic participants

ANOVA of AZ's RTs of correct decisions (factors *stimulus laterality, view* and *angle of rotation*) revealed a main effect for the factor *angle of rotation* ($F(3,141)=7.33$, $p<.01$) and significant interactions between the factors *view* and *angle of rotation* ($F(3,141)=4.31$, $p<.01$) and the factors *stimulus laterality* and *angle of rotation* ($F(3,141)=3.90$, $p=0.01$). RTs to hands presented upside down, i.e. 180°, were significantly slower than RTs to hands presented in all other angles of rotation ($t(77)>2.49$, $p<.01$). There was a palm view advantage exclusively for hands presented in a 180° rotation ($t(36)=3.50$, $p=.001$). Moreover, there was a right over left hand advantage exclusively for hands presented in a 270° rotation ($t(38)=3.06$, $p<.01$). Right hand RTs were significantly different for the following pairwise comparisons of angles of rotation: 0° vs 180°, 90° vs 270° and 180° vs 270° ($ts(37)>2.32$, $p<.01$). Left hand RTs differed for the comparisons 0° vs 180°, 90° vs 180° and 90° vs 270° ($ts(37)>2.01$, $p<.05$). The direction of these differences is displayed in Figure 5, left panel. Evidently, AZ showed a medial-lateral gradient for right and left hand stimuli (see Figure 18, left panel).

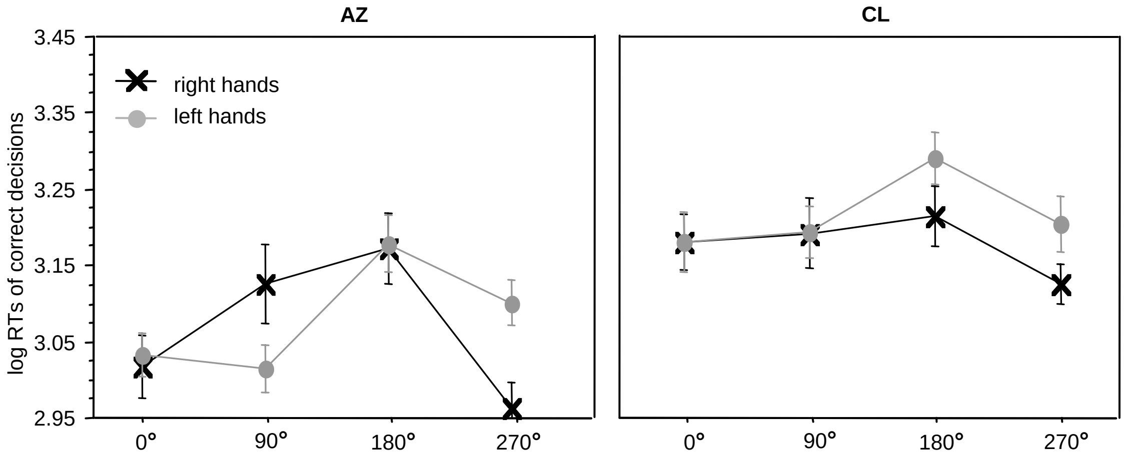

Figure 18. Significant interaction between *stimulus laterality* and *angle of rotation* in the participants with a bilateral hand amelia, the left panel displays the results of participant AZ with phantom sensations, the right panel the results of participant CL without phantom sensations. Displayed are means ± standard errors.

An analogous ANOVA of CL's RTs of correct decisions revealed significant main effects for the factors *angle of rotation* ($F(3,129)=3.83$, $p=0.01$) and *view* ($F(1,129)=41.2$, $p<.001$). CL favored the recognition of backs of hands over palms ($t(143)=6.04$, $p<.001$), and his RTs to hands presented under an angle of 180° were significantly longer than to those presented under an angle of 270° ($t(69)=2.48$, $p<.05$). There was no significant medial-lateral gradient, neither for left nor for right hands (Figure 18, right panel).

3.3.5. Discussion

In the present study we administered a hand laterality task to 14 persons who had been born with only one hand, to two persons born with no hands at all, and to 24 normally limbed control persons. We aimed at investigating whether the physical presence of a hand is necessary for the visual-somesthetic interactions typically demonstrated by healthy observers in this type of task. These interactions comprise (1) superior performance for pictures of hands corresponding to the observer's dominant hand, at least for right-handed populations; (2) a back-over-palm view advantage for hands presented with fingers pointing up and to either side, but not for those with fingers pointing down; (3) a medial-lateral gradient of the RTs of correct decisions, i.e. faster responses to hands with fingers pointing toward as compared to away from the body's midsaggital plane. All these previously reported effects could be replicated in the present population of normally limbed control persons (see Table 6), and once again support the view that (right) handedness and, more generally, biomechanical joint constraints are important determinants of left-right decisions regarding visually presented hands. We immediately proceed to a discussion of the presence or absence of such constraints in the participants with hand amelia, first addressing the findings in the group with *unilateral* congenital deficiencies.

Those 14 subjects with only one hand missing showed as clear a back-over-palm recognition advantage, as did normally limbed observers. Also, and again in correspondence with the data from the control group, RTs of correct decisions increased with larger angular deviations (up to 180°) of the displayed hand stimuli away from a prototypical (canonical) hand with its fingers pointing up. Over both hands, then, implicit matching of a representation of one's own hand with the orientation of a stimulus hand seems to be responsible for the gradual increase of task difficulty with increasing orientational incompatibility between the visual display and the momentary posture of one's own response hand (Funk, Wilkening et al., 2005). The life-long physical absence of one hand manifested itself in the fact that hand stimuli depicting the hand that was preserved (a left hand for subjects of the absR group and a right hand for the absL group) were significantly faster recognized than pictures of a hand corresponding to the missing one. This effect cannot be an artifact of a relatively unskillful or otherwise hampered response effector on the side of the stump or prosthesis, because there were not any RT differences for these same effectors as long as the target stimuli were left or right driving cars – control stimuli that obviously lack a corporeal representation in the human brain. It may be explained by pointing out that unilaterally amelic participants implicitly moved the only hand representation they had acquired in order to match it with the visual stimulus. A satisfactory match would immediately allow a positive laterality decision ("yes, it is the hand I am moving"); a no-match after a lengthy trial period, on the other hand, would eventually lead to the conclusion "if I can't match the shown hand, it must be the one I don't have". Such a disconfirmation strategy was already considered by Nico et al. (2004, pp. 128-129) in the face of their preliminary data with 3 congenital amputees (all with a missing left limb; Table 1). Whatever strategy ultimately most effective, the left hand recognition advantage of our subjects with an absent right hand deserves a comment. To our knowledge, such an advantage has not been previously shown for any subject group, left-handers and right-arm amputees included (Gentilucci et al., 1998; Nico et al., 2004). The finding is thus indicative of a strong ontogenetic influence of hand motor capabilities (i.e. physical hand use) on the central representation of a limb. However, a lifelong physical practice with only one hand does not seem to entirely disrupt one's response to the visual observation of pictures of the other hand. Remarkably, the participants with only one hand showed a medial-lateral gradient not only for hand pictures representing their normally developed hand, but also for those depicting the hand they had never felt, seen nor used for any action. This finding contrasts with data reported by Nico et al. (2004), whose 3 amelic subjects showed a medial-lateral gradient for the right (present), but not the left (congenitally absent) hand. These authors' conclusion that congenital limb absence "precludes the ability to produce joint-constrained mental simulations for the deleted hand" (p. 128) may have been unwarranted and based on the data from not enough subjects. We can only speculate about the apparent paradox resulting from the disadvantageous responding to hands depicting the absent limb (speaking for a weaker central representation of that hand) and the preserved medial-lateral gradient (reflecting an influence of the awkwardness of a hand position on the speed of the visual-somesthetic integration), thus speaking in favor of an intact hand representation. One possibility is that the symmetry of the medial-lateral gradients for the two hands may be responsible for the bilateral preservation of the effect in the participants with unilateral congenital hand absence. Again, a disconfirmation strategy based on an implicit motor imagery of the hand for which sensorimotor impressions have been collected could at least in part be responsible for the observed RT patterns.

The data obtained with the unilateral limb deficient participants do not allow making any strong claim regarding the validity of theories of innate components of the body schema (e.g., Berlucchi & Aglioti, 1997; Melzack, Israel, Lacroix, & Schultz, 1997; Price, 2006). The mechanisms of interhemispheric communications between the two sensorimotor cortices (e.g., Kobayashi, Hutchinson, Schlaug, & Pascual-Leone, 2003) have not yet been thoroughly delineated, nor do we know much about possible diaschisis effects - inhibitory or releasing - in the presence of unilateral peripheral limb absence. We had originally planned to study unilaterally amelic participants' performance in the hand laterality task as a function of phantom status, i.e. whether or not they had experienced phantom sensations of their absent limb. However, despite careful, non-suggestive questioning (Valentin, 1836; Brugger & Funk, in press), we could not find one person with aplasic phantoms in our study population. We note, however, that even if we had been successful, performance differences between participants with and without phantom sensations would not have told us enough to unambiguously decide between the views of an innate body schema on the one hand (Melzack et al., 1997) and that of a developmental genesis on the other. It was correctly pointed out (Brugger et al., 2000; Price, 2006) that the origin of phantom sensations of congenitally absent limbs in unilaterally amelic persons can always be claimed to be bound to the presence of an intact counterpart (Burchard, 1965; Grouios, 1998).

For these reasons, the data provided by AZ and CL deserve special attention. As these two persons have never owned even one single hand, any effects of implicit motor imagery as reflected in the performance in hand laterality tasks might tell us about the components of body schema that were not acquired by habitual physical execution of hand movements. To facilitate our discussion of these persons' performance, Table 6 summarizes the main effects and interactions found in the individual analyses.

Table 6. Significant main effects and interactions (+: present; -: absent) found in the 3-way ANOVA of the RTs of correct decisions in the hand laterality task with the factors angle of rotation (0°, 90°, 180°, 270°), stimulus laterality (left or right hand) and view (back of hands or palm).

	Main effects:			Interactions:			
Observers	I: angle of rotation	II: stimulus laterality	III: view	I x II	II x III	I x III	I x II x III
AZ;with phantoms	+	-	-	+	-	+	-
CL; without phantoms	+	-	+	-	-	-	-
commonly reported for normally limbed observers (e.g. Parsons, 1987)	+	+	+	+	-	+	+
normally limbed observers of the present study	+	+	+	+	-	+	+

As evident from Table 6, both participants with bilaterally missing hands showed one effect also known from normally limbed observers, that is, a main effect for angle of rotation. Specifically, hands with fingers pointing down were slower responded to than hands with fingers pointing up. In AZ, this effect was previously demonstrated (Brugger et al., 2000) and interpreted as evidence for the genuineness of her phantom sensations. The present study allows recognizing that this interpretation had not been justified. The observation of that effect in AZ doesn't allow any conclusions concerning the body-schema or motor-kinesthetic strategies involved in tasks requiring right/left judgments of rotated body parts as non-body related objects' rotation produces the same response pattern (Shepard & Metzler, 1971). A second argument challenging Brugger et al.'s (2000) interpretation is the finding that CL also showed the same effect, yet he has never had any phenomenal experience of the existence of hands. It would thus seem that the "inversion effect" (longer RTs to stimulus hands 180° rotated) does not depend (1) on the physical presence of hands, or (2) on the presence of phantom sensations of physically absent hands. Rather, a hand with fingers pointing upwards appears to represent a visually canonical view, as it is known for most objects. Such canonical orientations are typically accompanied by faster RTs (e.g. Palmer, Rosch, & Chase, 1981; Ashton et al., 1978).

The evaluation of further statistical relevant effects and interactions as revealed in the two bilaterally amelic subjects and the comparison with the response pattern repetitively described in normally limbed subjects may give further information about the genuineness of AZ's phantom sensations.

Neither AZ nor CL showed a preference in recognizing right or left hands. One could have expected an advantage in recognizing right over left hands as reported from right handed healthy subjects, at least for AZ as she previously provided evidence reflecting "right-handedness" (Brugger & Funk, in press). As CL uses his right foot, which he notably feels as and calls his right hand, for all daily activities it is likely that he would also have shown an advantage in recognizing right hands. CL, however, responded equally fast to right and left hands and we assume, likewise in consideration with AZ's data, that only the physically experience of a right hand results in an advantage in recognizing right hands.

An advantage in recognizing backs of hands over palms was previously described in normally limbed controls, at least when subjects were holding their hands in a regular palm down posture (Shenton et al., 2004; Funk, Wilkening, & et al., 2005). It seems that the proprioceptively defined hand position markedly influences the coding of hand position during mental motor imagery. As CL's but not AZ's data conveyed an advantage for judging backs of hands over palms, we suggest that in CL's case the propioceptive input of his right foot which he held in a sole down posture for responding may have been responsible for this effect.

Most important in the context of this study was the evaluation of the interaction between *stimulus laterality* and *angle of rotation* of which the medial-lateral gradient is the crucial aspect. The medial-lateral gradient reflects longer RTs to stimulus hands depicting laterally directed, awkward postures and shorter RTs to stimulus hands depicting medially directed, more comfortable hand postures. We found significant gradients for both hands for normally limbed control subjects and for AZ, but not for CL. While the absence of any gradient in the case of CL speaks for the necessity of sensorimotor experiences with hands, its presence in AZ refutes this contention. Here, a history of phantom sensations, in her case dating from very early childhood, may be the decisive factor. AZ reports that while phantom hand reflex movements (as e.g. reaching for a handrail) occasionally follow anatomically impossible trajectories, most other voluntary and involuntary phantom limb movements would be naturally constrained by joint biomechanics. In fact, we have recently shown that AZ's, but not CL's apparent motion perception of upper limbs is influenced by the range of movement that can actually be executed (Funk, Shiffrar et al., 2005). The interaction between *view* and *angle of rotation*, also significant for normally limbed participants and AZ but not for CL, adds more evidence for the facilitative effects of phantom limb sensations on motor imagery processes.

In summary, our experiment revealed that observers' performance on a hand laterality task is influenced in complex ways by the congenital absence of a hand. A clear handedness effect was found in unilaterally amelic persons, for whom the hand that was absent was also the one more difficult to reach a perceptual judgment when presented as a visual stimulus. Some joint constraints had an influence not only on decisions regarding the physically developed hand, but also regarding the absent hand. Finally, in the two participants born with neither a left nor a right hand, no handedness effects were evident, but biomechanical joint constraints influenced hand laterality decisions of specifically the one person with a history of phantom sensations. Together these results indicate that a lifelong use of one hand can facilitate motor imagery processes regarding the other hand and that the presence of phantom sensations is an important factor in the motor imagery regarding congenitally absent limbs.

One passing observation may finally need a comment, although it is not directly related to the topic of the present paper. In the group of 14 persons with unilateral congenital absence of a hand, 9 participants were lacking a left, and 5 a right hand (recall also that all 3 patients of Nico et al., 2004, had a left-sided deficiency). Despite these small numbers, we note that the almost two-fold incidence of left-sided deficiencies is probably no coincidence. Reviews of birth defects affecting the upper limbs regularly document this lateral asymmetry. Scotland and Galway (1983; their Table 1) described 69 absL children and only 43 absR children, without however commenting the imbalance. Simmel (1961; footnote 6) did comment on the 17:7 ratio in her sample, but only by noting that the asymmetry, though probably "real", remains unexplained among embryologists and orthopedic surgeons. To our knowledge, it has remained unexplained up to these days, a fact that emphasizes the importance of future research in the ontogenesis of amelia.

Together with work on motor imagery in persons with amelia, such research could provide important insights into the development of body schema and the genesis of phantom sensations of congenitally absent limbs.

3.4. Study 4: Hand movement observation by individuals born without hands: Phantom limb experience constrains visual limb perception

3.4.1. Abstract

Increasing evidence suggests that the visual analysis of other people's actions depends upon the observer's own body representation or schema. This raises the question of how differences in observers' body structure and schema impact their perception of human movement. We investigated the visual experience of two persons born without arms, one with and the other without phantom sensations. These participants, plus six normally limbed control observers, viewed depictions of upper limb movement under conditions of apparent motion. Consistent with previous results (Shiffrar and Freyd, 1990), normally limbed observers perceived rate-dependent paths of apparent human movement. Specifically, biologically impossible motion trajectories were reported at rapid display rates while biologically possible trajectories were reported at slow displays rates. The aplasic individual with phantom experiences showed the same perceptual pattern as control participants while the aplasic individual without phantom sensations did not. These preliminary results suggest that phantom experiences may constrain the visual analysis of the human body. These results further suggest that it may be time to move beyond the question of whether aplasic phantoms exist and instead focus on the question of why some people with limb aplasia experience phantom sensations while others do not. In this light, the current results suggest that somestheic representations are not sufficient to define body schema. Instead, neural systems matching action observation, action execution and motor imagery likely contribute to the definition of body schema in profound ways. Additional research with aplasic individuals, having and lacking phantom sensations, is needed to resolve this issue.

3.4.2. Introduction

Studies of phantom limbs after amputation have provided revolutionary insights into the neural plasticity of the human brain (Ramachandran and Hirstein 1998;

Halligan 2002, for reviews). These studies have also revealed that the "body in the brain" (Berlucchi and Aglioti 1997) or "body schema" is a highly flexible central representation of the human body. More generally, research with amputees has reminded us that "[w]e stand to learn most from phantoms if we attend closely to patients' subjective reports" (Halligan et al. 1999, p. 587). Indeed, the quantity and quality of cortical reorganization can be critically related to detailed characteristics of an individual's phantom limb experience (e.g., Flor et al. 1998; Knecht et al. 1998).

In striking contrast to the rapid pace with which our understanding of the perceptual and neural correlates of limb amputation unfolds, stands the near absence of experimental investigations of phantom limb phenomena in persons with limb aplasia. This may be due to the fact that many authors still doubt the very existence of "congenital phantoms" (e.g., Flor et al. 1998; Skoyles 1990). Indeed, the implicit assumption that phantom sensations of congenitally absent limbs cannot exist has resulted in studies of limb representation in aplasic people that lack reports of phantom sensations (e.g., Nico et al. 2004). Nonetheless, in the clinical literature, phantoms of congenitally absent limbs have been documented for well over a century (e.g., Valentin 1836; Poeck 1964; Burchard 1965; Grouios 1996). Relevant overview articles indicate that approximately 10% (Boonstra et al. 2000) to 20% (Weinstein et al. 1964; Melzack et al. 1997) of individuals born without limbs experience phantoms of their missing limbs. Apart from the high incidence of pain in post-amputation phantoms, which contrasts with a virtual absence of painful congenital phantoms (Melzack et al. 1997), the phenomenologies of the two types of phantoms are comparable. In both cases, postural and movement sensations predominate (e.g., Poeck 1969; Melzack et al. 1997) while thermal sensations are rare (e.g. Lacroix et al. 1992). Importantly, visual inspection of other peoples' bodies can trigger phantom sensations in amputees (e.g. Henderson & Smith 1948) and people with limb aplasia (Melzack et al. 1997). For example, Melzack and colleagues (1997) reported the case of a 14-year old boy with a missing right forearm and hand, whose phantom hand percept could be elicited by "playing with his friends and looking at their arms" (p. 1610).

These cross-modal interactions between the visual observation of other people's bodies and the observer's own body schema form the topic of the present report. Some authors (see especially Melzack, 1990) have taken the very existence of phantom sensations of limbs that have never physically developed as unshakable evidence for innate components of body schema. The ultimate utility of such conclusions may depend upon how one defines the term “body schema.” Growing evidence from behavioral (Reed and Farah 1995; Sebanz et al. 2003) and neuroimaging (Grèzes and Decety 2001) studies suggests that representations of one's own bodily actions share a common neural substrate with visual representations of the actions performed by other people. Such findings suggest that the "body schema" may be best understood as a multimodal representation of one's own body that contains input from somatosensory, proprioceptive, and vestibular systems as well as visual information about human body dynamics.

Here we investigate the perceptual, specifically visual, experience of two people with bilateral congenital absence of arms during the presentation of other peoples' upper limb movements. The rareness of bilateral arm aplasia, especially when accompanied with phantom sensations, precluded investigation of a larger group of subjects. We used a paradigm introduced by Shiffrar and Freyd (1990) in which observers watch pairs of photographs depicting a human model performing simple actions. The two photographs differ only in the position of one limb segment relative to a joint, and their rapid alternation gives rise to an apparent motion percept. As long as the two photographs are flashed in rapid succession, normal observers invariably perceive the displaced limb traversing the shortest possible path of visual apparent motion. Execution of a limb movement along this seen trajectory is, however, not anatomically possible as it would violate natural joint constraints. However, as the presentation rate slows, observers increasingly perceive paths of apparent limb movement that follow natural human limb trajectories (Shiffrar and Freyd 1990; 1993). Apparently, stored kinesthetic knowledge about possible movements constrains the visual perception of human movement provided ample processing time is provided for cross-modal sensorimotor-visual interaction. In line with this interpretation, neuroimaging data have revealed motor and parietal cortex involvement at slow, but not rapid presentation rates (Stevens et al. 2000). This psychophysical paradigm seemed ideally suited to quantitatively investigate interactions between phantom limb sensation and limb movement observation.

Two persons with limb aplasia were tested. While both are highly comparable in physical appearance and intelligence, they differ crucially in their experiences of their missing limbs. One participant reports vivid phantom sensations of missing arms and hands (Brugger et al. 2000), while the other has never experienced any phantom sensations whatsoever. If the experience of phantom limbs by individuals born without those limbs reflects visually based modifications of the body schema, and if visual perception of other people's actions depends upon the observer's own body schema, then one would expect to find that the two participants in the current study differ in their visual perception of other people's actions. Specifically, one would predict that the individual who experiences phantoms of congenitally missing arms would exhibit normal, rate-dependent percepts of apparent arm movement while the individual who does not experience arm phantoms would not.

3.4.3. Materials and methods

3.4.3.1. Participants

Participant one, AZ, is a 46-year old woman born without legs and with two short upper arms without elbow joints. Since her early youth, AZ has experienced phantom sensations of her missing body parts that include both voluntary and involuntary movements of her phantom arms. Her phantom reflex movements occasionally follow anatomically impossible trajectories. These occur, for instance, when reaching for a handrail in a tramcar that abruptly stops. In this case, her phantom hand is experienced "at the place of action", that is, where her upper arm stump actually touches the handrail. Intentionally induced hand and arm movements are always experienced as part of the anatomically possible repertoire of intact upper limbs. In a previous study, voluntary movement of AZ's phantom fingers activated premotor and parietal cortex with the greatest activation in the contralateral hemisphere (Brugger et al. 2000). As to interactions between feeling and seeing a limb, we note that it has occurred to AZ that contemplation of her mirror image abolishes her phantom sensations. AZ's vision is normal. She holds a university degree and works as a consultant for handicapped individuals. The etiology of her limb deficiencies is unknown.

Participant two, CL, is a 43-year old man born with shortened legs and absent arms (no shoulder articulations). In daily life, he uses his right foot for writing, eating, pointing, and gesturing. CL has not suffered any visual or cognitive impairment in the course of the thalidomide-related embryopathy. The skillful use of his right foot enabled him to have a successful career as a journalist. Importantly, CL has never experienced any phantom sensations of his missing limbs.

We also tested six normally limbed control observers (further on "intact observers") who were carefully matched by age and education to AZ and CL, respectively. All eight subjects gave written informed consent to participate in the experiment, which was performed in accordance with the Declaration of Helsinki.

3.4.3.2. Stimuli and procedure

The stimulus set was similar to that used by Shiffrar and Freyd (1990). Six stimulus pairs each consisting of two black and white photographs were used. The picture pairs depicted the starting and ending positions of the following arm and hand actions: (1) a man rotating in right hand about his wrist (Figure 19a), (2) the same for a woman's left hand, (3) the front view of a man rotating his left forearm about his elbow such that his hand is seen at the 11-o'clock and 8-o'clock positions, (4) the same for a woman's right forearm, (5) the side view of a man rotating his left arm backwards about his shoulder with the hands shown at the 2-o'clock and 4-o'clock positions and (6) the same for a woman's right arm.

Stimuli were presented in the center of a computer screen (software MacProbe; Hunt 1994) and subtended approximately 15° of visual angle both horizontally and vertically from the participants' viewing position. On each trial, the two photographs of each stimulus pair were presented for 90ms each and separated by one of four inter-stimulus intervals (ISIs), i.e. 135 ms, 435 ms, 735 ms and 1035 ms. These ISIs were selected because they yielded the most consistent apparent motion percepts in pilot studies with healthy volunteers. Each stimulus pair was presented 4 times, once with each ISI. For each participant, the sequences of stimulus pairs and ISIs were pseudo-randomized across trials. Each trial consisted of 12 cycles of alternation between the two photographs. Immediately following each trial, the participants indicated their perceived path of apparent motion on a response sheet (Figure 19A). As in Shiffrar and Freyd (1990, 1993), two possible paths of apparent motion were depicted on the response sheet. The short, physically impossible path was always labelled "A". The longer, physically possible path was labelled "B". Although two additional response options included the possibility of seeing "both A and B" paths and "neither A nor B" paths, participants were encouraged to primarily decide between options A and B.

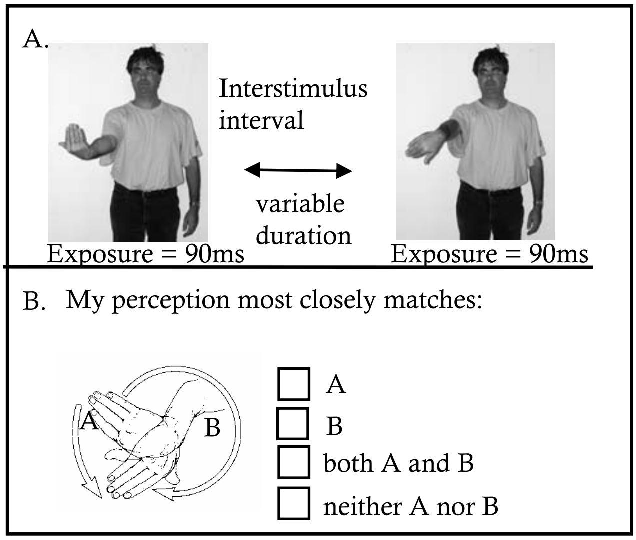

Figure 19 A.) A sample stimulus pair that normally produces an apparent rotation of the hand rotating about the wrist at long ISIs. The arrow indicates that the two photographs in each pair were sequentially flashed in rapid alternation (12 cycles with an inter-stimulus interval of 135 ms, 435 ms, 735 ms or 1035 ms). B.) Response sheet (for the sample stimulus displayed in A.) with which observers indicated, after each trial, what option best described their percept on that trial.

3.4.4. Results

For each of the eight volunteers, the percentages of trials during which they reported perceiving the short, impossible “A” path of apparent motion and the long, possible “B” path of apparent motion were determined at each ISI. The proportion of short to long paths is displayed in Figure 2. The six intact observers perceived the short, anatomically impossible paths of apparent limb motion at the 135 ms and 435 ms ISIs. Conversely, at the longer 735 ms and 1035 ms ISIs, these same participants were more likely to perceive the longer, anatomically possible paths of apparent limb rotation. Consistent with previous results (e.g., Shiffrar and Freyd, 1990), all six intact observers produced this same pattern of apparent motion perceptions. We calculated the slope of the linear regression line for each of these subjects. The boundaries of the respective 95% confidence interval are -.219 and -.132.

The two participants with limb aplasia, however, reported divergent patterns of apparent motion perception. AZ's perceived paths of apparent motion depended upon ISI in the same manner as path perception depended upon ISI for intact observers. AZ perceived the short, anatomically impossible paths of apparent limb motion at the 135 ms ISI and longer, anatomically possible paths at 1035 ISI. At the 735 ISI AZ favored neither the anatomically possible nor the anatomically impossible path. The slope of her linear regression is -.143 and thus lies within the intact observers' confidence interval.

Conversely, CL consistently perceived the short, anatomically impossible paths of apparent arm/hand rotation at all ISIs. The slope of his linear regression is - .008 and thus outside the confidence interval of intact observers.

We further calculated, for each ISI, the intact observers' 95% confidence interval for the mean proportion of short to long path percepts. AZ's data lie within the boundaries formed by these control participants' responses, except at the ISI of 435 ms. In contrast, CL's data lie outside these boundaries except at the ISI of 435 ms (Figure 20). The percentages of "A and B" and "Neither A nor B" responses across all ISIs were 13.5% (SD = 8.7%) for the controls and 16.7% and 12.5% for participants AZ and CL, respectively.

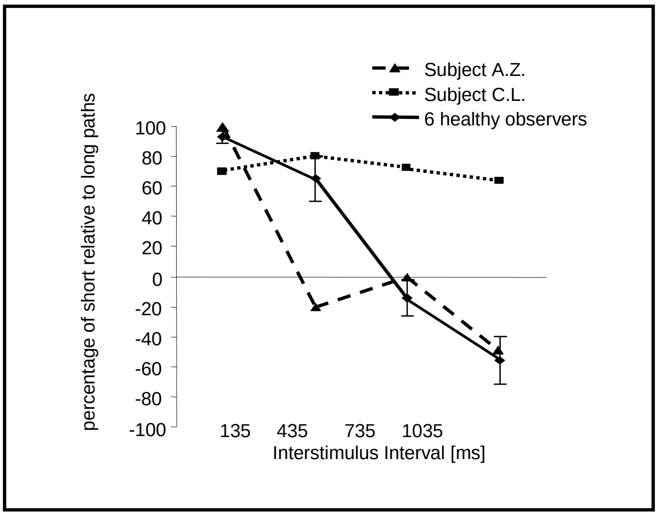

Figure 20. Difference between percentage of short (A in Figure 19B.) and long (B in Figure 19B.) paths of apparent motion plotted as a function of inter-stimulus interval. Data are averaged over the six different stimulus pairs. Solid line shows data from six intact observers (mean + 95% confidence intervals).

3.4.5. Discussion

Six intact observers showed the kinaesthetically modulated perceptions of apparent limb motion as first described in Shiffrar and Freyd (1990). While rapid display rates, or short ISIs, triggered the visual perception of short, anatomically impossible trajectories, longer ISIs allowed stored knowledge about natural joint mechanics to constrain perceived paths of apparent limb motion. This implicit biasing of what is seen by what is possible given biomechanical limitations of the human body was also observed for AZ, but not for CL.

On first consideration, the current results may appear surprising since AZ was born without hands and forearms and therefore has never executed any movements with these body parts. Since her early youth, however, she has experienced vivid phantom sensations of all missing body parts including individual fingers. Importantly, while AZ does not report the experience of pain or temperature in her phantoms, she does report highly vivid postural and movement sensations in them (Brugger et al. 2000). Our previous quantification of AZ's phantom movement sensations also involved a limb laterality task based on Parsons (1994). In this task, observers report whether a visually depicted hand or foot comes from the right or left side of the body. Intact observers showed longer reaction times whenever stimuli differ by larger physical rotations from their own corresponding body parts. AZ's data showed the same pattern; namely, longer reaction times for stimuli requiring a 180° rotation of her phantoms. These findings, together with those of the present experiment, strongly suggest that years of phantom movement experience may impose similar constraints on the visual analysis of human body stimuli as do years of sensorimotor experience with physically intact limbs. In addition, the current results indicate that, just like observers with intact bodies, AZ's visual processing is influenced by kinesthetic body schema information.

The causality underlying this potential cross-modal interaction between phantom limb sensation and the visual analysis of body motion is unclear. One could argue that AZ's visual perception of human movement is constrained by innate information about kinesthetic properties of the human body (Melzack 1990; Melzack et al. 1997). Alternatively, the proprioceptive or kinesthetic components of the body schema per se need not be innate. It is conceivable that somatic phantom sensations in people with congenital limb aplasia arise from activations of a system matching action observation and action execution (Grèzes and Decety 2001; Rizzolatti et al. 2001; Stevens et al., 2000). Anecdotal clinical observation (Melzack et al. 1997) is in fact compatible with the view that limb movement observation may be a prerequisite for the development of limb movement sensations. On the other hand, long-term limb observation alone cannot dictate the presence or absence of phantom sensations. If it did, then all sighted persons with limb aplasia would report such sensations. Thus, what remains to be understood is why only a minority of people with limb aplasia experience congenital phantoms.

The finding that CL's visual perception of apparent limb movements is timing independent emphasizes the importance of each individual’s history of phantom sensations (recall that CL has never experienced phantoms of his congenitally absent limbs). Interestingly, CL’s timing independent perception of apparent limb rotations in the current task concurs with his absence of a regular reaction time pattern in limb laterality tasks (Funk 2001). However, these results do not help us to identify the factors that determine whether or not a person with limb aplasia will develop congenital phantoms. We are currently studying the functional neuroanatomy of AZ's and CL's action observation system to find out whether the neural circuits known to be involved in normally limbed individuals (e.g., Buccino et al. 2001) are differently engaged in aplasic persons. It is conceivable that limb observation triggers limb sensation only in those aplasic persons whose neural circuitry allows for a rich integration of motor representations and their visual counterparts. Recent work on premotor cortex contributions to feelings of ownership for a visually observed limb may be relevant here (Ehrsson et al. 2004).

In summary, our preliminary data show that phantom sensations of congenitally absent limbs can influence the visual perception of other peoples' bodies in much the same way, as does a lifelong use of physically developed limbs. These results should be corroborated in a larger sample of persons with limb aplasia and leave several pressing questions to be addressed. First, are the performance differences described in the present study reflected in activation differences, primarily of the motor and parietal cortex, during limb movement observation (Stevens et al. 2000)? Second, is the presence/absence of intact biological motion processing accompanied by structural changes in areas of the motor cortex? Such changes have been reported in some

(Gowers 1879), but not other (Hamzei et al. 2001) individuals with congenital limb deficiencies. Lastly, how does the congenital absence of a single arm constrain participants' perceptions of hand movement? This question is interesting independent of participants' histories of phantom sensations (see Funk and Brugger 2002; Nico et al. 2004), and is especially important with respect to traditional theories concerning the origins of congenital phantoms (e.g. Valentin 1836; Burchard 1965; Grouios 1996). These theories suggest that, in unilateral amelia, phantom sensations of a missing arm could arise from sensorimotor representations of its existing counterpart.

4. CONCLUDING REMARKS

The aim of my thesis was to provide empirical evidence for the developmental and pathological influence on corporal representation in the human brain. The examination of children, persons with congenitally missing hands and healthy (normally limbed) control participants offered a unique and extensive access to study the issue of plasticity of the body representation in M1 and of the body schema, i.e. a higher-order body representation. The converging evidence from these investigations, including brain imaging and behavioral explorations, supported the general hypothesis of cerebral plasticity, the lifelong ability of the brain to reorganize neural pathways based on new experiences. Each of the four studies contributed to the delineation of the factors, which determine how and under which circumstances changes in the body representation are taking place.

4.1. Plasticity of both body representations in M1 and body schema

The aim of the first study was to document changes in the body schema during brain development. We found that the interaction between the two main sensory inputs, namely vision and proprioception, providing on-line feedback to the body schema was different in children and adults. In both, the immature and mature brain, visual and proprioceptive inputs seem to be relevant for the body schema, but in children the influence of proprioception appears to be stronger than in adults. This finding is in line with the notion (as e.g. popularized by Piaget, 1954) that perceptual and sensorimotor processes are more tightly linked in young children than in adults.

The core of this thesis was, however, the discovery of changes in the body representations due to a congenital absence of a body part. Focusing on neuroanatomy as well as on function, our investigations of persons with a unilateral absence of a hand since birth allowed some conclusions on behavior-brain interaction. By using fMRI, a method to study anatomo-functional correlations, convincing evidence for the plastic characteristic of M1 could be documented. The plastic organization of our nervous system seems optimal in such that not only neuronal networks can migrate but also that they serve for functional compensation. We found evidence for this efficiency in cases of a congenital absence of one hand, where the deafferented/deefferented cortical space [dedicated in normally limbed subjects to the motor control of hands] does not stay inactive. Apparently, in amelic persons' brain the adjacent orofacial motor area has invaded this deafferented/deefferented "hand" area (see Figure 21).

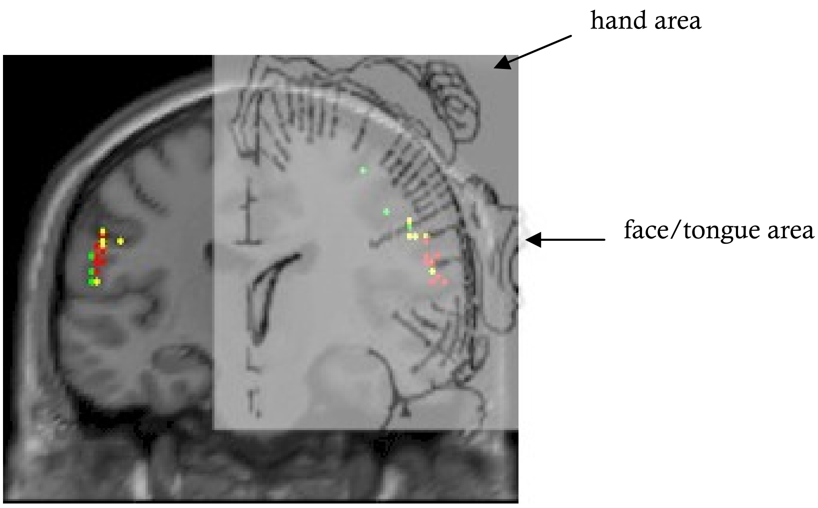

Figure 21. Motor tongue representation in controls (red blobs) and in unilaterally amelic participants (yellow indicates left hand amelia, green indicates right hand amelia)

Obviously, M1 not only reacts to traumatic amputation [notably in amputees with phantom limb pain] in the form of a cortical reorganization (e.g. Karl et al., 2001) but also responds similarly to the congenital absence of a limb.

We further rounded off the picture of body representation in unilaterally hand amelic participants by questioning whether we would also find evidence for an altered higher-order body representation (body schema). If this were the case, amelic subjects would perform differently from normally limbed participants in a hand laterality task. As we found that both groups solved this task similarly we concluded that the amelics have a "normal" body schema representing both the missing and the existing hand. Notably, a recent publication has questioned such a possibility on the basis of only three investigated amelic (all with left-sided absence) persons (Nico et al., 2005). In the same study evidence for an impaired body schema of traumatically amputated persons was found.

The question remains why amelic subjects showed an altered body representation in M1 but an apparently regular body schema. One could speculate that the sensorimotor experience of the existing hand together with the visual input of intact hands perceived in others were sufficient to complete and to develop a normal body schema, although with no effect on the anatomy of M1. Additional information to answer this question could be gained by examining subjects with one congenitally absent hand but for which a phantom is experienced on the phenomenal level. As these persons are very rare, such an approach is hardly realistic and this model remains largely theoretical. One could hypothesize that in unilaterally amelics with phantoms neuronal activity in the primary motor hand area (or at least in the associated premotor areas) would be seen, when they are moving the phantom hand. Consequently, their body representation in M1 would not significantly differ from normally limbed controls', as the neurons in the hand motor area subserved the phantom sensations of the missing hand. Also the performance of unilaterally amelics with phantoms in a task assessing higher body schema functions is difficult to delineate on theoretical grounds. On the one hand, one could hypothesize that they would perform similar to amelics without phantoms as performance is constrained by the properties of the physical rather than the mental body. Another speculation, however, would be that their task performance exceeded that of those individuals with a complete physical body, but, no history of phantom sensations. This latter view would tie in with previous speculations relating certain body schema operations in laboratory tasks to the spontaneous experience of a phantom. In the words of Sekiyama (1982; p. 95) "... it is conceivable that the mental representations generated in such a situation [hand laterality tasks] might share some properties in common with what is called 'phantom limb' ".

Even though the chance to test unilaterally amelics with phantom sensations escaped us, we had the unique opportunity to examine one subject (AZ) with congenitally missing arms and legs and vivid phantom sensations of these missing body parts. Her behavioral results were compared to those of a person, CL, who has similar amelic symptoms but no phantom sensations. AZ's performance was highly comparable to that of normally limbed controls, while CL's results differed. While this result clearly demonstrated that aplasic phantom sensations could constrain and guide the visual analysis of limb movements, it could not address one of the most prominent questions, why some people with limb aplasia develop phantom sensations and others do not. On the basis of our investigations with AZ, we can put forward several statements. The results introduced in this dissertation …

- … ruled out that AZ's phantoms are the product of wishful thinking or “pure” imagination [inconsistent with Sohn's 1914 and Skoyles' 1990 proposal]; mere fantasies cannot account for the distinctive pattern in motor reaction times to picture body parts that reflect time-consuming, biomechanically constrained motor imagery processes (see our Study 3).
- … allowed a falsification of theoretical proposals to account for aplasic phantoms, at least in their most general form: AZ has neither upper nor lower limbs [inconsistent with Burchard's 1965 suggestion to conceive of phantoms as a representation of the intact, contralateral limb], nor does she have any rudiments of distal body parts attached to her stumps [inconsistent with Simmel's 1961 "theory of rudiments"], yet experiences phantoms of all missing body parts.
- … suggested that AZ’s brain stores sensorimotor representations of hands and feet that are automatically activated during motor imagery conditions (fMRI experiments in Brugger et al., 2000) and on visual observation of other people moving their limbs (see our Study 4).
- … most generally evidenced that even though the physical appearance of humans' body is identical, their mental body representation can considerably differ.

However, our findings do not solve the puzzle about the genesis of aplasic phantoms. They can only help to shape future empirical research.

4.2. The genesis of aplasic phantoms: a tough nut to crack

Even though we presented new data in this thesis, the genesis of phantom sensation in aplasia must thus remains a puzzle. They strongly suggest, however, that body schema has both innate and acquired components and that the latter may also rely on visual processing. We act on the idea that the body schema comprises neural systems matching action observation, action execution and motor imagery. The strongest candidate for the existence of this mechanism is the mirror neuron system (Rizzolatti et al., 2001). It has been reported that mirror neurons in the monkey (located in area F5 in the ventral premotor cortex) are activated when a monkey performs an action as well as when it observes the same action executed by the experimenter (Gallese & Goldman, 1998). Also in humans, the existence of an analogous mirror system was demonstrated (Fadiga, Craighero & Olivier, 2005). An explanation for the genesis of phantoms sensations could be that the observation of body use in others could trigger phantom experiences in amelics, whose brains are wired in a way enabling the integration between the innate motor representation and its visual counterparts. It is thus conceivable that differences in the matching of an observed movement with an imagined execution of this movement may reveal the condition subserving the development of phantoms. To simplify, phantom limb sensations could arise from learning by observation. Thus, the finding of a mirror neuron system may be crucial to understand the existence of aplasic phantoms (see also Price, 2006). Specifically designed prospective studies comparing the brain activation pattern of AZ and CL during limb movement observation will be necessary for further elucidating this issue.

4.3. Direction of future research

In the next year, further research with amelic participants dealing with the following questions will be conducted:

- How is the body representation in M1 organized in participants with bilaterally missing hands? Will also an enlargement of the adjacent tongue area as observed in unilaterally amelic participants (Study 1) be find? How will the neural substrates underlying the special behavioral characteristics (i.e. writing with the mouth or gesturing with the foot) of the bilaterally amelic participants look like? In order to answer these questions, fMRI data from AZ and CL will be collected.
- Does the observation and imagery of hands in subjects with unilateral or bilateral hand amelia differ from normally limbed controls'? It is known that in normally limbed participants mere the observation or imagery of hand movements is sufficient to activate motor neurons in the brain. Do we find the same cortical motor activations if an amelic person observes or imagines the missing hand? Is the vivid experience of the own hand a premise for finding motor activations during motor hand observation or imagery task? With the application of fMRI during the performance of motor observation and imagery, answers to those questions should be found.

5. REFERENCES

Alkadhi, H., Crelier, G.R., Boendermaker, S.H., Golay, X., Hepp-Reymond, M.C., & Kollias, S.S. (2002). Reproducibility of primary motor cortex somatotopy under controlled conditions. *American Journal of Neuroradiology, 23,* 1524-1532.

Ashburner, J., & Friston, K.J. (1999). Nonlinear spatial normalization using basis functions. *Human Brain Mapping, 7,* 254-266.

Ashton, R., McFarland, K., Walsh, F., & White, K. (1978). Imagery ability and the identification of hands: A chronometric analysis. *Acta Psychologica, 42,* 253-262.

Berlucchi, G., & Aglioti, S. (1997). The body in the brain: neural bases of corporeal awareness. *Trends in Neuroscience, 20,* 560-564.

Bertenthal, B.I., & Clifton, R.K. (1998). Perception and action. In D. Kuhn & R.S. Siegler (Eds.), *Handbook of child psychology, Vol 2: Cognition, perception, and language* (pp. 51-102). New York: Wiley.

Berti, A., Bottini, G., Gandola, M., Pia, L., Smania, N., Stracciari, A., et al. (2005). Shared cortical anatomy for motor awareness and motor control. *Science, 309,* 488-491.

Bonda, E., Petrides, M., Frey, S., & Evans, A. (1995). Neural correlates of mental transformations of the body-in-space. *Proceedings of the National Academy of Sciences of the USA, 92,* 11180-11184.

Boonstra, A.M., Rijnders, L.J., Groothoff, J.W., & Eisma, W.H. (2000). Children with congenital deficiencies or acquired amputations of the lower limbs: functional aspects. *Prosthetics and Orthotics International, 24,* 19-27.

Brugger, P., & Funk M. (in press). Out on a limb: facts and fallacies in the study of "aplasic phantoms". In S. della Sala (Ed.), T*all Tales about the Brain. Things we Think we Know about the Mind, but ain't so*. London: Wiley.

Brugger, P., Kollias, S.S., Müri, R.M., Crelier, G., Hepp-Reymond, M.-C., & Regard, M. (2000). Beyond re-membering: phantom sensations of congenitally absent limbs. P*roceedings of the National Academy of Sciences of the USA, 97,* 6167-6172.

Brugger, P. & Regard, M. (1998). Phantom limbs in congenital tetramelia: a case report. *Journal of the International Neuropsychological Society, 4,* 206.

Buccino, G., Binkofski, F., Fink, G.R., Fadiga, L., Fogassi, L., Gallese, V., et al. (2001). Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *European Journal of Neuroscience, 13,* 400-404.

Burchard, J.M. (1965). Zur Frage nach der Natur von Phantomerlebnissen bei angeborener Gliedmassenverstümmelung. *Archiv für Psychiatrie und Zeitschrift für die gesamte Neurologie, 207,* 360-377.

Buxbaum, L.J., & Coslett, H.B. (2001). Specialised structural descriptions for human body parts: Evidence from autotopagnosia. *Cognitive Neuropsychology, 18,* 289-306.

Buxbaum, L.J., Giovannetti, T., & Libon, D. (2000). The role of the dynamic body schema in praxis: evidence from primary progressive apraxia. *Brain and Cognition, 44,* 166-191.

Buxbaum, L.J., Sirigu, A., Schwartz, M.F., & Klatzky, R. (2003). Cognitive representations of hand posture in ideomotor apraxia. *Neuropsychologia, 41,* 1091-1113.

Campbell, J.J. (2000). Neuropsychiatric assessment. In C.E. Coffey & J.L. Cummings (Eds.), *Textbook of Geriatric Neuropsychiatry* (2nd ed., pp. 109-124). Washington, DC: American Psychiatric Press.

Cedrus Corporation (2002). SuperLab Pro (Version 2.0) [Computer software]. San Pedro, CA: Author.

Chapman, L.J., & Chapman, J.P. (1987). The measurement of handedness. *Brain and Cognition, 6,* 175-183.

Cohen, M.S., Kosslyn, S.M., Breiter, H.C., DiGirolamo, G.J., Thompson, W.L., Anderson, A.K., et al. (1996). Changes in cortical activity during mental rotation. A mapping study using functional MRI, *Brain, 119,* 89-100.

Cooper, L.A., & Shepard, R.N. (1975). Mental transformations in the identification of left and right hands. *Journal of Experimental Psychology. Human Perception and Performance, 1,* 48-56.

Corfield, D.R., Murphy, K., Josephs, O., Fink, G.R., Frackowiak, R.S., Guz, A., et al. (1999). Cortical and subcortical control of tongue movement in humans: a functional neuroimaging study using fMRI. *Journal of Applied Physiology, 86,* 1468-1477.

Coslett, H.B. (1998). Evidence for a disturbance of the body schema in neglect. *Brain and Cognition, 37,* 527-544.

Coslett, H.B., Saffran, E.M., & Schwoebel, J. (2002). Knowledge of the human body: A distinct semantic domain. *Neurology, 59,* 357-363.

Critchley, M. (1953). Disorders of the body-image. In M. Critchley (Ed.), *The parietal lobe* (pp. 225–55). New York: Hafner Press.

Cruz, V.T., Nunes, B., Reis, A.M., & Pereira, J.R. (2003). Cortical remapping in amputees and dysmelic patients: a functional MRI study. *NeuroRehabilitation, 18,* 299-305.

Curt, A., Alkadhi, H., Crelier, G.R., Boendermaker, S.H., Hepp-Reymond, M.C., & Kollias, S.S. (2002). Changes of non-affected upper limb cortical representation in paraplegic patients as assessed by fMRI. *Brain, 125,* 2567-2578.

De Vignemont, F., Zalla, T., Posada, A., Louvegnez, A., Koenig, O., Georgieff, N., & Franck, N. (2006). Mental rotation in schizophrenia. *Consciousness and Cognition*, *15,* 295-309.

Di Russo, F., Committeri, G., Pitzalis, S., Spitoni, G., Piccardi, L., Galati, G., et al. (2006). Cortical plasticity following surgical extension of lower limbs. *Neuroimage, 30,* 172-183.

Dominey, P., Decety, J., Broussolle, E., Chazot, G., & Jeannerod, M. (1995). Motor imagery of lateralized sequential task is asymmetrically slowed in hemi-Parkinson's patients. *Neuropsychologia, 33,* 727-741.

Ehrsson, H.H., Spence, C., Passingham, R.E. (2004). That's my hand! Activity in premotor cortex reflects feeling of ownership of a limb. *Science, 305,* 875-877.

Elbert, T., & Rockstroh, B. (2004). Reorganization of human cerebral cortex: the range of changes following use and injury. *Neuroscientist, 10,* 129-141.

Fiorio, M., Tinazzi, M., & Aglioti, S.M. (2006). Selective impairment of hand mental rotation in patients with focal hand dystonia. *Brain, 129,* 47-54.

Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumer, N., et al. (1995). Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature, 375,* 482-484.

Flor, H., Elbert, T., Mühlnickel, W., Pantev, C., Wienbruch, C., & Taub, E., 1998. Cortical reorganization and phantom phenomena in congenital and traumatic upper-extremity amputees. *Experimental Brain Research, 119,* 205-212.

Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.P., Frith, C.D., & Frackowiak, R.S.J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping, 2,* 189-210.

Friston, K.J., Worsley, K.J., Frackowiak, R.S.J., Mazziotta, J.C., & Evans, A.C. (1994). Assessing the significance of focal activations using their spatial extent. *Human Brain Mapping, 1,* 210-220.

Funk, M. (2001). Mentale Rotation von Händen und körperfremden Objekten: Untersuchungen mit Kindern und Erwachsenen mit und ohne kongenitalem Handmangel. Master's thesis, University of Zurich, Faculty of Philosophy, Department of Experimental and Developmental Psychology

Funk, M., & Brugger, P. (2002). Visual recognition of hands by persons born with only one hand. *Cortex, 38,* 860-863.

Funk, M., Shiffrar, M., & Brugger, P. (2005). Hand movement observation by individuals born without hands: Phantom limb experience constrains visual limb perception. *Experimental Brain Research, 164,* 341-346.

Funk, M., Wilkening, F., & Brugger, P. (2005). Motor processes in children's kinaesthetic imagery. *Developmental Science, 8,* 402-408.

Gallagher, S., Butterworth, G., Lew, A., & Cole J (1998). Hand-mouth coordination, congenital absence of limb, and evidence for innate body schemas. *Brain and Cognition 38,* 53-65.

Gallagher, S., & Cole, J. (1995). Body image and body schema in a deafferented subject. *Journal of Mind and Behavior, 16,* 369–390.

Ganis, G., Keenan, J.P., Kosslyn, S.M., & Pascual-Leone, A. (2000). Transcranial magnetic stimulation of primary motor cortex affects mental rotation. *Cerebral Cortex, 11,* 175-180.

Gentilucci, M., Daprati, E., & Gangitano, M. (1998). Right-handers and left-handers have different representations of their own hand. *Cognitive Brain Research, 6,* 185–192.

Gerstmann, J. (1930). Zur Symptomatologie der Hirnläsionen im Übergangsgebiet der unteren Parietal- und mittleren Occipitalwindung, *Nervenarzt, 3,* 691-695.

Giraux, P., Sirigu, A., Schneider, F., & Dubernar, J.M. (2001). Cortical reorganization in motor cortex after graft of both hands, *Nature Neuroscience, 4,* 691-692.

Gowers, W.R. (1879). Clinical cases. The brain in congenital absence of one hand. *Brain, 1,* 386-390.

Grezes, J., & Decety, J. (2001). Functional anatomy of execution, mental simulation, observation, and verb generation of actions: a meta-analysis. *Human Brain Mapping, 12,* 1-19.

Grouios, G. (1996). Phantom limb perceptuomotor 'memories' in a congenital limb child. *Medical Science Research, 24,* 503-504.

Grouios, G. (1998). Phantom limb sensations: a review. *Medical Science Research, 26*, 219-223.

Haggard, P., & Wolpert, D.W. (2005). Disorders of body scheme. In H.J. Freund, M. Jeannerod, M. Hallett & R. Leiguarda (Eds.), *Higher-order motor disorders*. (pp. 261-271). Oxford University Press.

Halligan, P.W. (2002). Phantom limbs: the body in mind. *Cognitive Neuropsychiatry, 7,* 251-268.

Halligan, P.W., Zeman, A., & Berger, A. (1999). Phantoms in the brain. Question the assumption that the adult brain is "hard wired". *British Medical Journal, 319,* 587-588.

Hamzei, F., Liepert, J., Dettmers, C., Adler, T., Kiebel, S., Rijntjes, M., et al. (2001). Structural and functional cortical abnormalities after upper limb amputation during childhood. *NeuroReport, 12,* 957-962.

Head, H., & Holmes, G. (1911). Sensory disturbances from cerebral lesions. *Brain, 34,* 102-254.

Henderson WF, Smyth GE, 1948. Phantom limbs. *Journal of Neurology, Neurosurgery, and Psychiatry, 11*, 88-112.

Hesselmann, V., Sorger, B., Lasek, K., Guntinas-Lichius, O., Krug, B., Sturm, V., et al. (2004). Discriminating the cortical representation sites of tongue and lip movement by functional MRI. *Brain Topography, 16,* 159-167.

Hunt, S.M.J. (1994). MacProbe: a Macintosh-based experimenter's workstation for the cognitive sciences. *Behavior Research Methods, Instruments and Computers, 26,* 345-351.

Jackson, J.H. (1958). On the anatomical and physiological localisation of movements in the brain. In J. Taylor, G. Holmes & F.M.R. Walshe (Eds.), *Selected Writings of John Hughlings Jackson. On Epilepsy and Epileptiform Convulsions* (Vol. 1, pp. 37-76). New York: Basic Books.

Jensen, T.S., Krebs, B., Nielsen, J., & Rasmussen, P. (1985). Immediate and long-term phantom limb pain in amputees: incidence, clinical characteristics and relationship to pre-amputation limb pain. *Pain, 21,* 267-278.

Johnson, S.H., Sprehn, G., & Saykin, A.J. (2002). Intact Motor Imagery in Chronic Upper Limb Hemiplegics: Evidence for Activity-Independent Action Representations. *Journal of Cognitive Neuroscience, 14,* 841-852.

Kail, R., Pellegrino, J., & Carter, P. (1980). Developmental changes in mental rotation. *Journal of Experimental Child Psychology, 29,* 102-116.

Kamping, S., Lutkenhoner, B., & Knecht, S. (2004). Shifting of cortical somatosensory areas in a man with amelia. *Neuroreport, 15,* 2365-2368.

Karl, A., Birbaumer, N., Lutzenberger, W., Cohen, L.G., & Flor, H. (2001). Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. *The Journal of Neuroscience, 21,* 3609-3618.

Knecht, S., Dräger, B., Deppe, M., Bobe, L., Lohmann, H., Flöel, A., et al. (2000). Handedness and hemispheric language dominance in healthy humans. *Brain, 123,* 2512-2518.

Knecht, S., Hennigsen, H., Höhling, C., Elbert, T., Flor, H., Pantev, C., et al. (1998). Plasticity of plasticity? Changes in the pattern of perceptual correlates of reorganization after amputation. *Brain, 121,* 717-724.

Kobayashi, M., Hutchinson, S., Schlaug, G., & Pascual-Leone, A. (2003). Ipsilateral motor cortex activation on functional magnetic resonance imaging during unilateral hand movements is related to interhemispheric interactions. *NeuroImage, 20,* 2259-2270.

Korkman, M., Kirk, U., & Kemp, S. (1998). A developmental neuropsychological assessment (NEPSY): Manual. San Antonio, TX: The Psychological Corporation

Kosslyn, S.M. (1994). *Image and brain.* Cambridge, MA: MIT Press

Kosslyn, S.M., Digirolamo, G.J., Thompson, W.L., & Alpert, N.M. (1998). Mental rotation of objects versus hands: Neural mechanisms revealed by positron emission tomography. *Psychophysiology, 35,* 151-161.

Kosslyn, S.M., Margolis, J.A., Barrett, A.M., Goldknopf, E.J., & Daly, P.F. (1990). Age differences in imagery abilities. *Child Development, 61,* 995-1010.

Kosslyn, S.M., Thompson, W.L., Wraga, M., & Alpert, N.A. (2001). Imagining rotation by endogenous versus exogenous forces: Distinct neural mechanisms. *NeuroReport, 12,* 2519-2525.

Lacroix, R., Melzack, R., Smith, D., & Mitchell, N. (1992). Multiple phantom limbs in a child. *Cortex, 28,* 503-507.

Levine, S.C., Huttenlocher, J., Taylor, A., & Langrock, A. (1999). Early sex differences in spatial skill. *Developmental Psychology, 35,* 940-949.

Lotze, M., Flor, H., Grodd, W., Larbig, W., & Birbaumer, N. (2001). Phantom movements and pain. An fMRI study in upper limb amputees. *Brain, 124,* 2268-2277.

Lotze, M., Seggewies, G., Erb, M., Grodd, W., & Birbaumer, N. (2000). The representation of articulation in the primary sensorimotor cortex. *Neuroreport, 11,* 2985-2989.

Marmor, G.S. (1975). Development of kinetic images: When does the child first represent movement in mental images? *Cognitive Psychology, 7,* 548-559.

Marmor, G.S. (1977). Mental rotation and number conservation: Are they related? *Developmental Psychology, 13,* 320-325.

Marquart, M., Birn, R., & Haughton, V. (2000). Single- and multiple-event paradigms for identification of motor cortex activation. *American Journal of Neuroradiology, 21,* 94-98.

Martin, R.E., MacIntosh BJ, Smith RC, Barr AM, Stevens TK, Gati JS, Menon RS, 2004. Cerebral areas processing swallowing and tongue movement are overlapping but distinct: a functional magnetic resonance imaging study. *Journal of Neurophysiology 92,* 2428-2443.

Mattay, V.S., Weinberger, D.R. (1999). Organization of the human motor system as studied by functional magnetic resonance imaging. *European Journal of Radiology, 30,* 105-114.

Melzack, R. (1989). Phantom limbs, the self and the brain: The D. O. Hebb memorial lecture. *Canadian Psychology, 30,* 1-16.

Melzack, R. (1990). Phantom limbs and the concept of a neuromatrix. *Trends in Neuroscience, 13,* 88-92.

Melzack, R., Israel, R., Lacroix, R., Schultz, G. (1997). Phantom limbs in people with congenital limb deficiency or amputation in early childhood. *Brain, 120,* 1603-1620.

Montoya, P., Ritter, K., Huse, E., Larbig, W., Braun, C., Topfner, S., et al. (1998). The cortical somatotopic map and phantom phenomena in subjects with congenital limb atrophy and traumatic amputees with phantom limb pain. *European Journal of Neuroscience, 10,* 1095-1102.

Moseley, G.L. (2004a). Why do people with complex regional pain syndrome take longer to recognize their affected hand? *Neurology, 62,* 2182-2186.

Moseley, G.L. (2004b). Graded motor imagery is effective for long-standing complex regional pain syndrome-a randomised controlled trial. *Pain, 108,* 192-198.

Moseley, G.L., Sim, D.F., Henry, M.L., & Souvlis, T. (2005). Experimental hand pain delays recognition of the contralateral hand-evidence that acute and chronic pain have opposite effects on information processing? *Cognitive Brain Research, 25,* 188-194.

Münte, T.F., Altenmüller, E., & Jäncke, L. (2002). The musician's brain as a model of neuroplasticity. *Nature Reviews Neuroscience, 3,* 473-478.

Nico, D., Daprati, E., Rigal, F., Parsons, L., & Sirigu, A. (2004). Left and right hand recognition in upper limb amputees. *Brain, 127,* 120-132.

Nissan, J., Gross, M.D., Shifman, A., Tzadok, L., & Assif, D. (2004). Chewing side preference as a type of hemispheric laterality. *Journal of Oral Rehabilitation, 31,* 412-416.

Nudo, R.J., Plautz, E.J., & Frost, S.B. (2001). Role of adaptive plasticity in recovery of function after damage to motor cortex. *Muscle & Nerve, 24,* 1000-1019. Review

Palmer, S.E., Rosch, E., & Chase, P. (1981). Canonical perspective and the perception of objects. In J. Long & A. Baddeley (Eds.), Attention and Performance, IX (pp. 135-151). Hillsdale, N J: Lawrence Erlbaum.

Parsons, L.M. (1987). Imagined spatial transformations of one's hands and feet. *Cognitive Psychology, 19,* 178–241.

Parsons, L.M. (1994). Temporal and kinematic properties of motor behavior reflected in mentally simulated action. *Journal of Experimental Psychology. Human Perception and Performance, 20,* 709-730.

Parsons, L.M., Fox, P.T., Downs, J.H., Glass, T., Hirsch T.B., Martin C.C., et al. (1995). Use of implicit motor imagery for visual shape discrimination as revealed by PET. *Nature, 375,* 54-58.

Parsons, L.M, Gabrieli, J.D., Phelps, E.A., & Gazzaniga, M.S. (1998). Cerebrally lateralized mental representations of hand shape and movement. *The Journal of Neuroscience, 18,* 6539-6548.

Pearce, A.J., Thickbroom, G.W., Byrnes, M.L., & Mastaglia, F.L. (2002). Functional reorganization of the corticomotor projection to the hand in skilled racquet players. *Experimental Brain Research, 130,* 238-243.

Penfield, W. & Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain, 60,* 389-443.

Penfield, W. & Rasmussen, T. (1950). *The Cerebral Cortex of Man,* New York: MacMillan

Perner, J. (1991). *Understanding the representational mind.* Cambridge, MA: MIT Press.

Piaget, J. (1954). *The construction of reality in the child*. New York: Basic Books.

Piaget, J., & Inhelder, B. (1971). *Mental imagery in the child*. New York: Basic Books.

Picard, C., & Olivier, A. (1983). Sensory cortical tongue representation in man. *Journal of Neurosurgery, 59,* 781-789.

Pick, A. (1915). Zur Pathologie des Bewusstseins vom eigenen Körper: Ein Beitrag aus der Kriegsmedizin, *Neurologisches Centralblatt, 34,* 257-265.

Pick, A. (1922). Störung der Orientierung am Eigenen Körper. *Psychologische Forschung, 2,* 303-318.

Poeck, K. (1964). Phantoms following amputation in early childhood and in congenital absence of limbs. *Cortex, 1,* 269-275.

Poeck, K. (1969). Phantome nach Amputation und bei angeborenem Gliedmassenmangel. *Deutsche Medizinische Wochenschrift, 94,* 2367-2374.

Price, E.H. (2006). A critical review of congenital phantom limb cases and a developmental theory for the basis of body image. *Consciousness and cognition, 15,* 310-322.

Ramachandran, V.S., & Hirstein, W. (1998). The perception of phantom limbs: the D.O. Hebb Lecture. *Brain, 121,* 1603-1630.

Ratcliff, G. (1979) Spatial thought, mental rotation and the right cerebral hemisphere. *Neuropsychologia, 17,* 49-54

Reed, C.L., & Farah, M.J. (1995). The psychological reality of the body schema: A test with normal participants. *Journal of Experimental Psychology. Human Perception and Performance, 21,* 334-343.

Rizzolatti, G. & Craighero, L. (2004) The mirror-neuron system, *Annual Review of Neuroscience,* 27, 169-192.

Rizzolatti, G., Fogassi, L., & Gallese, V. (2001). Neurophysiological mechanisms underlying the understanding and imitation of action. *Nature Reviews Neuroscience, 2,* 661-670.

Rorden, C., Heutink, J., Greenfield, E., & Robertson, I.H. (1999). When a rubber hand 'feels' what the real hand cannot. *NeuroReport, 10,* 135-138

Rosenbaum, D.A., Carlson, R.A., & Gilmore, R.O. (2001). Acquisition of intellectual and perceptual-motor skills. *Annual Review of Psychology, 52,* 453-470.

Rumiati, R.I., Tomasino, B., Vorano, L., Umilta, C., & De Luca, G. (2001). Selective deficit of imagining finger configurations, *Cortex, 37,* 730-733.

Salmaso, D., Longoni, A.M. (1985). Problems in the assessment of hand preference. *Cortex, 21,* 533-549.

Sanes, J.N., & Donoghue, J.P. (2000). Plasticity and primary motor cortex. *Annual Review Neuroscience, 23,* 393-415.

Schwenkreis, P., Pleger, B., Cornelius, B., Weyen U, Dertwinkel R, Zenz M, et al. (2003). Reorganization in the ipsilateral motor cortex of patients with lower limb amputation. *Neuroscience Letters, 349,* 187-190.

Schwoebel, J., Boronat, C.B., & Coslett, H.B. (2002). The man who executed "imagined" movements: Evidence for dissociable components of the body schema. *Brain and Cognition, 50,* 1–16.

Schwoebel, J., & Coslett, H.B. (2005). Evidence for Multiple, Distinct Representations of the Human Body, *Journal of Cognitive Neuroscience, 17,* 543-553.

Schwoebel, J., Coslett, H.B., Bradt, J., Friedman, R., & Dileo, C. (2002). Pain and the body schema: effects of pain severity on mental representations of movements. *Neurology, 59,* 775-777.

Schwoebel, J., Friedman, R., Duda, N., & Coslett, H.B. (2001). Pain and the body schema: Evidence for peripheral effects on mental representations of movement. *Brain, 124,* 2098-2104.

Scotland T.R., & Galway H.R. (1983). A long-term review of children with congenital and acquired upper limb deficiency. *The Journal of Bone and Joint Surgery. British Volume, 65,* 346-349.

Sebanz, N., Knoblich, G., & Prinz, W. (2003). Representing others' actions: just like one's own? *Cognition, 88,* B11-B21.

Sekiyama, K. (1982). Kinesthetic aspects of mental representations in the identification of left and right hands. *Perception & Psychophysics, 32,* 89-95.

Shenton, J.T., Schwoebel, J., & Coslett, H.B. (2004). Mental motor imagery and the body schema: evidence for proprioceptive dominance. *Neuroscience Letters,* 370, 19-24.

Shepard, R.H., & Cooper, L.A. (1982). *Mental images and their transformations.* Cambridge, MA: MIT Press.

Shepard, R.N., & Metzler, J. (1971). Mental rotation of three-dimensional objects. *Science, 171,* 701-703.

Sherman, R.A., Sherman, C.J., & Parker, L. (1984). Chronic phantom and stump pain among American veterans: results of a survey. *Pain, 18,* 83-95.

Shiffrar, M., & Freyd, J.J. (1990). Apparent motion of the human body. *Psychological Science, 1,* 257-264.

Shiffrar, M., & Freyd, J.J. (1993). Timing and apparent motion path choice with human body photographs. *Psychological Science, 4,* 379-384.

Simmel, M.L. (1961). The absence of phantoms for congenitally missing limbs. *American Journal of Psychology, 74,* 467-470.

Sirigu, A., & Duhamel, J.R. (2001). Motor and visual imagery as two complementary but neurally dissociable mental processes. *Journal of Cognitive Neuroscience, 13,* 910-919.

Sirigu, A., Grafman, J., Bressler, K., & Sunderland, T. (1991). Multiple representations contribute to body knowledge processing. *Brain, 114,* 629-642.

Skoyles, J.R. (1990). Is there a genetic component to body schema? *Trends in Neuroscience, 13,* 409.

Sohn, D.L. (1914). The psychic complex in congenital deformity. *New York Medical Journal, 100,* 959-961.

Stevens, J.A., Fonlupt, P., Shiffrar, M., & Decety, J. (2000). New aspects of motion perception: selective neural encoding of apparent human movements. *NeuroReport, 11,* 109-115.

Stoeckel, M.C., Jorgens, S., Witte, O.W., & Seitz, R.J. (2005). Reduced somatosensory hand representation in thalidomide-induced dysmelia as revealed by fMRI. *European Journal of Neuroscience, 21,* 556-562.

Szirtes, J., & Vaughan, H.G. Jr. (1977). Characteristics of cranial and facial potentials associated with speech production. In J.E. Desmedt (Ed.), *Language and Hemispheric Specialization in Man: Cerebral Event-Related Potentials. Progress in Clinical Neurophysiology* (Vol. 3, pp. 112-116). Basel: S. Karger.

Tagaris, G.A., Richter, W., Kim, S.K., Pellizzer, G., Andersen, P., Ugurbil, K., et al. (1998). Functional magnetic resonance imaging of mental rotation and memory scanning: a multidimensional scaling analysis of brain activation patterns. *Brain research. Brain Research Reviews, 26,* 106-112.

Thayer, Z.C., Johnson, B.W., Corballis, C., & Hamm, J.P. (2001). Perceptual and motor mechanisms for mental rotation of human hands. *Cognitive Neuroscience and Neuropsychology, 12,* 3433-3437.

Thurstone, L.L. & Thurstone, T.G. (1941/1962). *Primary mental abilities.* Chicago: Science Research Associates.

Tomasino, B., Rumiati, R.I., & Umilta, C.A. (2003). Selective deficit of motor imagery as tapped by a left-right decision of visually presented hands. *Brain and Cognition, 53,* 376-380.

Tomasino, B., Toraldo, A., & Rumiati, R.I. (2003). Dissociation between the mental rotation of visual images and motor images in unilateral brain-damaged patients. *Brain and Cognition, 51,* 368-371.

Tomasino, B., Budai, R., Mondani, M., Skrap, M, & Rumiati, R.I. (2005). Mental rotation in a patient with an implanted electrode grid in the motor cortex. *Neuroreport, 16,* 1795-1800.

Tyc, F., Boyadjian, A., & Devanne, H. (2005). Motor cortex plasticity induced by extensive training revealed by transcranial magnetic stimulation in human. *European Journal of Neuroscience, 21,* 259-266.

Valentin, G. (1836). Über die subjektiven Gefühle von Personen, welche mit mangelhaften Extremitäten geboren sind. *Repertorium für Anatomie und Physiologie, 1,* 328-337.

Vingerhoets, G., de Lange, F.P., Vandemaele, P., Deblaere, K., & Achten, E. (2002). Motor imagery in mental rotation: An fMRI study. *NeuroImage, 17,* 1623-1633.

Weinstein, S., & Sersen, E.A. (1961). Phantoms in cases of congenital absence of limbs. *Neurology, 11,* 905-911.

Weinstein, S., Sersen, E.A., & Vetter, R.J. (1964). Phantoms and somatic sensation in cases of congenital aplasia. *Cortex, 1,* 276-290.

Wexler, M., Kosslyn, S.M., & Berthoz, A. (1998). Motor process in mental rotation. *Cognition, 68,* 77-94.

Wildgruber, D., Ackermann, H., Klose, U., Kardatzki, B., & Grodd, W. (1996). Functional lateralization of speech production at primary motor cortex: a fMRI study. *Neuroreport, 7,* 2791-2795.

Wilkening, F., & Huber, S. (2002). Children's intuitive physics. In U. Goswami (Ed.), *Blackwell Handbook of childhood cognitive development* (pp. 349-370). Oxford: Blackwell.

Yetkin, F.Z., Haughton, V.M., Cox, R.W., Hyde, J., Birn, R.M., Wong, E.C., et al. (1996). Effect of motion outside the field of view on functional MR. *American Journal of Neuroradiology, 17,* 1005-1009.

Zacks, J.M., Michelon, P., Vettel, J.M., & Ojemann, J.G. (2004). Functional reorganization of spatial transformations after a parietal lesion. *Neurology, 63,* 287-292

Zacks, J., Rypma, B., Gabrieli, J.D.E., Tversky, B., & Glover, G.H. (1999). Imagined transformations of bodies: an fMRI investigation. *Neuropsychologia, 37,* 1029-1040.

6. APPENDICES

Appendix 1: fMRI Abklärungsdokument

Name: Vorname: Adresse:

Telefon: e-mail: Geburtsdatum:

Geschlecht: weiblich ❐ männlich ❐, Händigkeit: re ❐ li ❐

Gegenwärtiger Beruf:......................................

Schulbildung: Oberschule ❐, Real/Sekundarschule ❐, Gymnasium ❐

Technikum, höhere Fachschule ❐, Universität, Hochschule ❐

Berufsausbildung: Keine ❐, Anlehre ❐, Lehre ❐

1. Würden Sie sich als klaustrophobisch (Angst vor engen Räumen) beschreiben?	Ja - Nein
2. Hatten Sie jemals eine Kopfverletzung mit Bewusstseinsverlust? Wenn ja, bitte erklären Sie welche und wie lange Sie bewusstlos waren	Ja - Nein
3. Hatten Sie schon einmal einen epileptischen Anfall oder Migräne?	Ja - Nein
4. Wurden Sie schon mal auf eine neurologische Krankheit hin abgeklärt?	Ja - Nein
5. Wurden Sie schon mal auf eine psychologische Krankheit hin abgeklärt?	Ja - Nein
6. Wurden Sie schon mal wegen einer Alkohol- oder Drogenabhängigkeit behandelt oder dachten Sie, dass sie eine Behandlung nötig hätten?	Ja - Nein
7. Nehmen Sie gegenwärtig irgendwelche Medikamente? Bitte listen Sie alle auf, auch solche, die nicht verschreibungspflichtig sind.	Ja - Nein
8. Trinken Sie Koffein? Wenn ja, wie viele Gläser oder Tassen durchschnittlich pro Tag?	Ja - Nein
9. Trinken Sie Alkohol? Wenn ja, wie viele dl. durchschnittlich pro Tag?	Ja - Nein
10. Rauchen Sie Zigaretten, Zigarren oder Pfeife? Wenn ja, wie viele Jahre rauchen Sie schon?____ Wie viele Zigaretten täglich im Durchschnitt?____	Ja - Nein
11. Befindet sich in Ihrem Körper Metall (Herzschrittmacher, Platten, Nägel?)	Ja - Nein
12. Hatten Sie schon einmal eine Augenverletzung mit Metallsplittern?	Ja - Nein
13. Haben Sie ein Body Piercing, das nicht entfernt werden kann?	Ja - Nein
14. Tragen Sie eine Spange, Zahnimplantate oder ein Gebiss?	Ja - Nein
15. Tragen Sie eine Brille oder Kontaktlinsen? Brille____, Linsen_____, kurzsichtig_____ weitsichtig_____	Ja - Nein
16. Sind Sie farbenblind?	Ja - Nein
17. Haben Sie eine Gehörschwäche?	Ja - Nein

Appendix 2: Children's handedness assessment (german adaptation from NEPSY by Korkman et al., 1998)

Anamnesefragebogen für Kindergartenkinder

VP NR:

Name:

Vorname:

Geburtsdatum:

Untersuchungsort:

Untersuchungsdatum:

Bestimmung der Händigkeit:

	Rechte Hand	Linke Hand
Zeichne einen Kreis		
Zeige die gelbe Kugel		
Setze sie auf den grössten Stab		
Nimm den rosa Kreis		
Wirf ihn in die Schachtel		
Total		

Appendix 3: Adults' handedness assessment, items of the shorten version of the Edinburgh handedness inventory as proposed by Salmaso and Longoni (1985)

Name:

Jahrgang: Geschlecht:

Für die folgenden Aktivitäten sollen Sie die Bevorzugung der rechten oder linken Hand angeben, indem Sie in der für Sie zutreffende Spalte ein Kreuz machen.
Für einige Aktivitäten benötigen Sie beide Hände. In diesen Fällen ist derjenige Teil der Handlung, für welche die Händigkeit zu bestimmen ist, in Klammern angegeben.
"Immer rechts" bzw. "immer links" bedeutet, dass Sie nur unter Zwang die andere Hand gebrauchen würden.
Bitte beantworten Sie alle Fragen

Welche Hand würden Sie brauchen?	Immer rechts	Keine Bevorzugung	Immer links
Schreiben			
Zeichnen			
Einen Ball werfen			
Mit einer Schere schneiden			
Zahnbürste			
Messer (ohne Gabel)			
Schwamm			
Einen Besen brauchen (obere Hand)			
Ein Streichholz anzünden (Streichholz)			
Einen Deckel öffnen (Deckel)			

Auswertung/Anzahl Punkte berechnen: Immer rechts (3) Keine Bevorzugung (2) Immer links (1)

Totale Summe:

7. CURRICULUM VITAE

Name:	Marion Funk
Born:	April 12, 1973 in Zurich, Switzerland
Citizen of:	Zurich, Switzerland
Private address:	Wildenstrasse 5, CH-8049 Zurich
Work address:	Department of Neurology, Neuropsychology Unit University Hospital Zurich, 8091 Zurich, Switzerland Phone:++41-1-255-5537, FAX: ++41-1-255-4429 E-mail: marion.funk@usz.ch

EDUCATION AND WORK EXPERIENCE

1980-1986	Primary and Secondary School in Zurich, Switzerland
1986-1992	High School (Kantonsschule Hohe Promenade) in Zurich, Switzerland
04.1993-10.1993	Commercial Education, Steiger Schule in Zurich, Switzerland
10.1993-09.1995	Traineeship at Union Bank of Switzerland (UBS) in Zurich, Switzerland
10.1995-09.2001	Study of Psychology at the University of Zurich, Zurich, Switzerland Major: General and Developmental Psychology 1st minor: Psychopathology, 2nd minor: Neuropsychology
10.2001	Master degree in Psychology (lic.phil. I) Master thesis: Mentale Rotation von Händen und körperfremden Objekten: Untersuchungen mit Kindern und Erwachsenen mit und ohne kongenitalem Handmangel [Mental rotation of hands and non body -related objects in healthy children and adults as well as in adults born with a missing hand]
04.2002-03.2006	Research and clinical assistant at the Department of Neurology, Neuropsychology Unit, University Hospital of Zurich (Heads of Neuropsychology Unit: Prof. Dr. phil. M. Regard und PD Dr. phil. P. Brugger)

03.2006	Ph.D University of Zurich, Department of Psychology and Neuroscience Centre of Zurich, Switzerland
04.2006-present	Post-doctoral fellow (independent research) at the Neuropsychology Unit, Neurological Department of the University Hospital of Zurich. Clinical neuropsychologist (insurance expertise)

OWN PUBLICATIONS

PAPERS

Funk, M., & Brugger, P. (2002). Visual recognition of hands by persons born with only one hand. *Cortex, 38,* 860-863.

Funk, M., Wilkening, F., & Brugger, P. (2005). Motor processes in children's imagery: The case of mental rotation of hands. *Developmental Science, 8,* 402-408.

Funk, M., Shiffrar, M., & Brugger, P. (2005). Hand movement observation by individuals born without hands: Phantom limb experience constrains visual limb perception. *Experimental Brain Research, 164*, 341-346.

SUBMITTED PAPERS AND PAPERS IN PREPARATION

Funk, M., Lutz, K., Hotz Boendermaker, S., Roos, M., Summers, P., Brugger, P., Hepp-Reymond, M.C., & Kollias S.S. (submitted). Alteration of the motor tongue representation in congenital absence of a hand. *Cerebral Cortex.*

Funk, M., & Brugger, P. (submitted). Mental rotation of congenitally absent hands. *Brain and Cognition.*

Funk, M., & Brugger, P. (in preparation). Language lateralization in congenital absence of one upper limb.

BOOK CHAPTER

Brugger, P., & Funk, M. (in press). Out on a limb: facts and fallacies in the study of "aplasic phantoms". In S. della Sala (Ed.). Tall Tales about the Brain. Things we Think we Know about the Mind, but ain't so. London: Wiley.

CONFERENCE PRESENTATION

Citable Abstracts

Funk, M., & Brugger, P. (2001). Visual recognition of hands by persons born with only one hand. Behavioural Pharmacology, 12, Suppl.1, 38.

Funk, M., Wilkening, F., & Brugger, P. (2001). Are backs of hands always faster recognized than palms? Behavioural Pharmacology, 12, Suppl.1, 38.

Other conference presentations

Funk, M., Brugger, P., & Wilkening, F. (2001). Wenn der Körper mitspielt: zur Entwicklung

der mentalen Rotation von Händen: Poster presented at the Congress of Developmental Psychology, Potsdam.

Funk, M., Hotz Boendermaker, S., Boeni, T., & Brugger, P. (2003). Use of a functional prosthesis alters painful and non-painful phantom sensations in leg amputees. Poster presented at the Symposium of the Neuroscience Center Zurich, Zurich.

Hotz Boendermaker, S., Funk, M., Summers, P., Hepp-Reymond, M.-C., Burrack, A., Brugger, P., & Kollias, S.S. (2003). Influence of objects on brain activation during action observation, Poster presented at the Symposium of the Neuroscience Center Zurich, Zurich.

Funk, M., Hotz Boendermaker, S., Lutz, K., Summers, P., Brugger, P., Hepp-Reymond, M.-C., & Kollias, S.S. (2004). Neural substrates of first- and third person motor imagery, Poster presented at the 34th Annual Meeting of the Society of Neuroscience, San Diego.

Funk, M., Lutz, K., Hotz Boendermaker, S., Summers, P., Brugger, P., Hepp-Reymond, M.-C., & Kollias, S.S. (2004). Cortical tongue representation in dysmelic patients, Poster presented at the Symposium of the Neuroscience Center Zurich, Zurich.

Funk, M., Weniger, D., & Brugger, P. (2004). Language lateralization in congenital absence of one upper limb, Poster presented at the Symposium of the Neuroscience Center Zurich, Zurich.

Funk, M. (2004). Cortical tongue representation in dysmelic patients, Data Blitz at the Symposium of the Neuroscience Center Zurich, Zurich.